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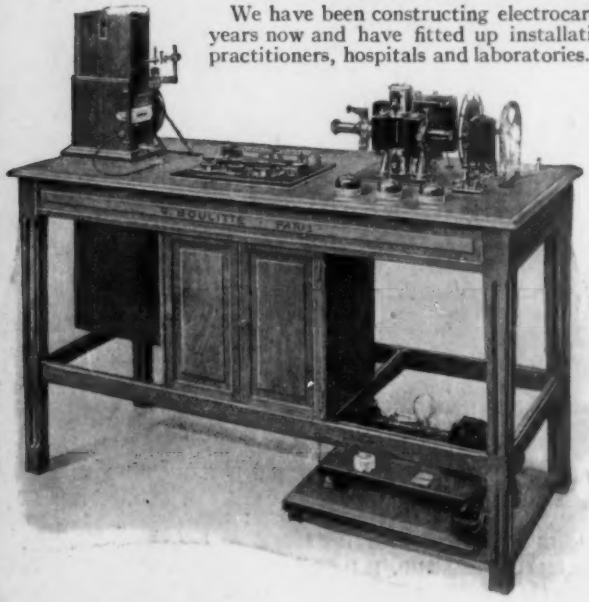

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THE

AMERICAN JOURNAL

OF THE MEDICAL SCIENCES

JANUARY, 1926

ORIGINAL ARTICLES.

SOME GENERAL FEATURES OF ENDOCRINE INFLUENCE ON METABOLISM.*

By W. B. Cannon, M.D.,

BOSTON.

(From the Department of Physiology, Harvard Medical School.)

A FAIRLY constant or steady state, maintained in many aspects of the bodily economy even when they are beset by conditions tending to disturb them, is a most remarkable characteristic of the living organism. Though the blood is the common carrier for all manner of food material and for waste, its composition varies to a surprisingly slight degree. Though warm-blooded animals are exposed to numerous and extensive alterations of surrounding temperature, they themselves undergo shifts of temperature within only a brief range. And though food is taken in as it is provided or desired and is utilized as conditions may demand, the body weight of the full-grown individual continues for long periods on a strikingly even level. Since in these, and in other instances which could be added to them, circumstances are often present which, if not controlled, would profoundly modify the constancy of the state, we must assume that controlling factors are at hand ready to act whenever the constancy is imperilled. The existence of steady states in the body and some agencies maintaining them have, of course, long been recognized. On this occasion I am laying emphasis upon these states because of an interest in some

* Read as one of the papers in a symposium on Internal Secretion, Congress of American Physicians, Washington, May 6, 1925.

tentative general considerations with regard to physiologic factors regulating them, and in the possible bearing of these considerations on problems of internal secretion. As they may have value in suggesting lines of research and bases for critical judgment, they may be worthy of attention.

Six Propositions Regarding Physiologic Factors Maintaining Steady States in the Body. The first proposition is that in an open system, such as our bodies represent, complex and subject to numberless disturbances, the very existence of a poised or steady state is in itself evidence that agencies are at hand keeping the balance, or ready to act in such a way as to keep the balance. These agencies may act antagonistically, like the nerves of the heart. A tonic action is also possible, as in arterial vasoconstriction, with constancy provided indirectly, one step back, in a nerve center subjected to opposed control. The regulation may consist of a check on the excesses of a continuous function, like the respiratory setting of the carbon-dioxide level in the blood. Again, there may be limitation by overflow, a safety-valve arrangement, as in the renal thresholds of overflow or escape for various constituents of the blood.

A second proposition is that, if the state remains steady, there is an automatic arrangement whereby any tendency toward change is effectively met by increased action of the factor or factors which resist the change. Somewhat similar statements of this proposal have been made by Spencer[1] and also by the Belgian physiologist, Fredericq.[2] They did not recognize, however, failure of the state to retain its poise because of absence or weakness of a controlling agent—a not uncommon consequence of pathologic processes. For that reason I have made the statement conditional ("if the state remains steady"). As Lotka[3] has pointed out, such a reservation, which is required for constant states in living beings, and which is a recognition of their lack of permanent stability, would sharply distinguish the proposal from the strict principle of Le Chatelier which was enunciated for physicochemical systems.

A third proposition is that any factor which operates to maintain a steady state by action in one direction does not act at the same point in the opposite direction. This declaration may appear tautological, but, as will be shown later, it has interesting bearings, and if its probable truth had been recognized it would have led to more cautious conclusions than have been drawn.

A fourth proposition, related to the third, is that factors which may be antagonistic in one region, where they effect a balance, may be coöperative in another region. It is necessary, therefore, to define closely the field of action of opposing factors in discussing a physiologic equilibrium.

A fifth proposition is that the system of checks which determines a balanced state may not be constituted of only two antagonistic

factors; on either side there may be two or more, brought into action at the same time or successively. Further, the two may be of different nature, for instance, an internal secretion and a neuromuscular agency.

A sixth proposition is that when a physiologic factor is known which can shift a steady state in one direction, it is reasonable to look for a physiologic factor or factors having a contrary or counterbalancing effect.

In the foregoing statements the expression "ready to act" has been used as an alternative to "acting" because in certain instances there is evidence that the situation is not kept balanced by direct and immediate opposition of active agencies, but is allowed to move to and fro within limits or within critical points, possibly under control of simple physicochemical adjustments, and only when these limits are passed are the more complex and indirect physiologic agencies (that is, those involving reactions peculiar to the organization of living beings) brought into play.

The advances in our knowledge of the relations of internal secretion to metabolism have lately been so great and so various that an attempt to present an encyclopedic survey in brief compass would be futile. Instead, may we not consider the six propositions, stated above, with regard to some recent investigations and results, and see to what degree interpretation is clarified thereby and new lines of work are indicated. In doing so I wish to disclaim any effort at an elaborate or final scheme of relationships. The concept of equilibrating factors will be used merely as a means of unifying some apparently diverse and separate observations which, in the main, have been personal experiences.

The Equilibrating Factors in the Blood-sugar Balance. Carbohydrate is the material most readily burned in the body. When it is provided in abundance the combustion of fat is almost completely stopped and the combustion of protein is reduced to a minimum. In less than half an hour after the ingestion of sugar the respiratory quotient usually rises to about 1.[4] The concurrent testimony of investigators supports the conclusion that carbohydrate is not only the most readily utilizable source of energy, but is essential for working the mechanism of muscular contraction. Its importance, therefore, need not be emphasized.

In the economics of the body, problems arise concerning carbohydrate demand and supply because that foodstuff is continuously being used up and is renewed only periodically. When it is taken in and is being digested it must not be permitted to increase in the blood above 170 or 180 mg. per 100 cc., for then it will be lost by escape through the kidneys. The amount available is likely to be more than is needed for current uses; the excess must be set aside in storage, in a compact and not immediately utilizable form. This is accomplished chiefly in the liver, though there are, of course,

the scattered local stores. When need arises the stored carbohydrate must be released from the liver, for if the glucose in the blood falls to approximately 45 mg., convulsions are likely to occur, which may be followed by coma and death. Thus, in sum, the blood-sugar level is an equilibrium between the supply and the demand, with storage as an adjusting arrangement. The normal outer limits of the equilibrium may be regarded as at approximately 180 mg. where loss occurs, and approximately 45 mg. where convulsions occur. But the normal variations of blood sugar are ordinarily well within these extreme limits. If our earlier propositions are correct, factors are at work, holding the oscillations inside the narrower confines. Some recent research done by McIver and Bliss and myself[5] has revealed a sympathico-adrenal mechanism as one factor in the balance, protecting the body against the dangers of too low blood sugar.

As an indicator of increased adrenal secretion we have used the heart, disconnected from the central nervous system and left in the body to perform its function. If the temperature is kept normal, only changes in the blood stream can affect the rate. Alterations of blood pressure do not influence it, but a very slight increase in the adrenin content of the blood promptly makes the heart beat faster. Anrep and Daly[6] have recently found that the denervated heart is sensitive to the presence of adrenin,* 1 part in 1,400,000,000 parts of blood. All investigators now admit that medulli-adrenal secretion is controlled by sympathetic impulses. Afferent stimulation and asphyxia, which are known to discharge sympathetic impulses, cause acceleration of the denervated heart—just such a change as is produced by increase of adrenin in the blood. The only agent which may confuse the response in an acute experiment is a substance given off from the liver after protein feeding—a source of trouble which can be made insignificant by study of a fasting animal or abolished by severing the hepatic nerves.[7] If these precautions are taken the positive response disappears when the adrenal glands are removed or inactivated by nerve section. The faster heart rate, therefore, is then due to medulli-adrenal secretion.[8] The results which we have obtained by use of the denervated heart have been questioned by Stewart and Rogoff.[9] These results, however, have been confirmed by Tournade and Chabrol[10] in Algiers, working with a crossed circulation; by Houssay and Molinelli[11] in Buenos Aires, also employing a crossed circulation; by Florovsky[12] and by Baschmakoff[13] in Odessa, using the denervated salivary gland, by Hartman, McCordock and Loder[14] in Buffalo, recording the reactions of the completely denervated iris; by Anrep[15,16] in London, studying the denervated heart and kidney and also the isolated heart outside the body but connected with the abdominal aorta and inferior vena cava. Furthermore, Kodama[16] in Sendai, Japan, repeating the procedure of Stewart

* The word "adrenin" is used to indicate the secretion of the adrenal gland; "adrenalin" a preparation of the same.

and Rogoff, has found, not what they found, but what we found. Naturally Stewart and Rogoff[17] have criticized Kodama's results, and have declared that he did not master their technic. A recent letter from Sendai, however, states that other workers there have refined the method, and that Kodama's data have been fully substantiated. If any investigator anywhere had given Stewart and Rogoff any support for their contention that adrenal secretion is constant, and unaffected by conditions which induce sympathetic activity, there might be reason for seriously considering it. But that support is lacking. Opposed to it is the concordant experience of other investigators, derived from a variety of methods. It justifies confidence in the results obtained by use of the denervated heart as a signal for greater discharge from the adrenal medulla.

Now to return to the question of a sympathico-adrenal factor working to keep the blood sugar normal and to protect the organism from dangerous hypoglycemia. Among the hypoglycemic reactions which occur when an excessive dose of insulin has been given are pallor, a rapid pulse, dilatation of the pupils and profuse sweating. These are phenomena resulting from sympathetic impulses. The denervated heart tells whether the adrenal medulla shares in this increased activity. When, after an injection of insulin, the glycemic concentration is falling, it reaches a critical point at which the denervated heart begins to beat faster. And as the sugar percentage continues to fall the heart rate continues to rise until a maximum is reached. In the unanesthetized test animal the critical point lies between 70 and 80 mg. of glucose per 100 cc. of blood—a concentration at which in man also hypoglycemic symptoms first appear.[18] The faster beating of the denervated heart indicates that medulli-adrenal secretion has been stimulated. That inference is verified by removal of the glands, or by removal of one and denervation of the other, whereupon a fall of the glycemic percentage below the critical point is not accompanied by a more rapid heart beat. The faster beating of the heart, of course, indicates that impulses are being discharged along splanchnic fibers. These sympathetic impulses, in coöperation with increased adrenal secretion, might be expected to call forth sugar from the liver. This inference is confirmed by the fact that as the rate of the denervated heart increases (manifesting sympathico-adrenal activity), the rate of falling of the glycemic percentage is checked. And if not too much insulin has been given, the glycemic percentage may not only cease dropping, but may rise to normal. A highly significant feature of this sympathico-adrenal activity is that as the blood-sugar level rises the activity subsides. Indeed, when glucose is injected intravenously the activity has been seen to subside completely within two minutes.

Here is a remarkable mechanism having the function of keeping up the physiologic percentage of blood sugar when there is danger

of deficiency. After a dose of insulin the mechanism may be brought into service hours before a convulsion occurs, and if effective it may wholly protect against a convulsion. From the evidence provided by these observations we may conclude that the lower inner limit of variation of blood sugar, when the sugar is being withdrawn, lies in the region of 70 to 80 mg. Reduction below this limit calls into action a sympathico-adrenal factor working to prevent further reduction. This factor works with increasing vigor the lower the glycemic percentage, until an acme is reached in a convulsion, when the denervated heart beats most rapidly.

According to Olmsted and Logan,[20] the convulsive seizures do not occur in a spinal animal, even when the glycemic percentage is extremely reduced. The sensitive region appears to be in the medulla or midbrain, for, in decerebrate animals typical convulsions result from hypoglycemia. Rapport and I[21] have shown that a center for medulli-adrenal secretion exists in the fore part of the floor of the fourth ventricle. Quite possibly this region is especially sensitive to a reduced sugar supply and by sympathico-adrenal discharges (culminating in spasms) protects the rest of the body against the hazards of too great a reduction.

Our results have received support from Abe,[22] who made use of the sensitized iris to signal a greater output from the adrenal medulla. In some instances he noted no effect, or very slight effect, during the first half-hour after giving insulin. Then there was a sudden change, marking the onset of the sympathico-adrenal function as the blood-sugar percentage fell. Houssay, Lewis and Molinelli[23] also have supported our conclusions. They employed a crossed circulation from the left adrenal vein of one dog to a jugular vein of another. When an insulin hypoglycemia was established in the donor, hyperglycemia was produced in the recipient—a result which did not occur if the left splanchnics of the donor had previously been severed. Both methods showed that adrenal secretion was increased by hypoglycemia, but unfortunately they were not used in such a way as to bring out the evidence for the critical point at which the sympathico-adrenal mechanism is set going, an observation of special interest in relation to the glycemic equilibrium.

In our second proposition we postulated that the preservation of a balanced state implies an automatic arrangement whereby a tendency to change is met by increased action of a factor or factors which resist the change. We have surveyed the evidence for a factor checking a shift of the glycemic equilibrium downward. What agency or agencies operate in the opposite sense, to prevent a shift upward, toward a high sugar concentration? The answer might be given promptly that it is the internal secretion of the pancreas, if competent investigators had not concluded that insulin

administered to normal animals is capable of decreasing hepatic glycogen, that is, that insulin may work in the same direction with the sympathico-adrenal mechanism. There is excellent reason for believing, however, that insulin primarily is the opposing factor and that its apparently anomalous effect in normal animals should be regarded as a secondary phenomenon. Let us examine the basis for the inference that the internal secretion of the pancreas, or insulin, normally protects the body against hyperglycemia by promoting sugar storage in the liver:

1. There is the outstanding fact that removal of the pancreas is promptly followed by hyperglycemia and a great reduction in the hepatic glycogen reserve. This phenomenon is so well known as to need no emphasis.

2. As Banting and his collaborators[24] have shown, the administration of insulin to depancreatized animals not only brings the blood sugar down to the normal level, but causes glycogen to accumulate again in large amounts in the hepatic cells. Indeed, the hepatic glycogen of insulin-treated diabetic animals may be considerably more than in normal well-fed controls.

3. It has been found that insulin will induce a deposit of glycogen in the liver when the blood sugar is within the range of normal variations. Thus, Cori[25] has recently reported that the amount of hepatic glycogen may be quadrupled in phlorizinized rabbits by repeated doses of insulin.

4. Finally, as bearing on the antagonism between the glycogenolytic action of adrenin and the glycogenetic action of insulin, there may be cited the experiments of McCormick, Noble and O'Brien.[26] They discovered that when large doses of adrenalin were injected—doses which produced a marked reduction of hepatic glycogen in control animals—the additional injection of insulin was accompanied by a striking retention of the hepatic glycogen. The excessive doses of adrenalin used by them (for example, 2.5 cc. in a rabbit) allowed, they state, "enormous quantities of insulin" (for example, 140 units) to be tolerated without convulsions.

All these various observations bear witness to the importance of the internal secretion of the pancreas (insulin) as an agent operating conversely to the sympathico-adrenal mechanism in affecting the glycemic percentage by action on the liver.

The suggestion that insulin does not act in one direction only but in both directions on the liver (that is, glycogenetically and glycogenolytically) has, to be sure, been derived from experiments on normal animals. McCormick and Macleod[27] gave insulin and carbohydrates to rabbits rendered free of glycogen and found that less glycogen was deposited in the livers of the insulin-treated animals. Dudley and Marrian[28] compared the livers of glycogen-rich mice and rabbits, some of which had received insulin and others left as controls; the hepatic glycogen of the former was very

greatly reduced as compared with the latter. Babkin[29] also has reported that the glycogen content of the liver in well-nourished rabbits which had been given insulin is markedly lowered. The comments on these experiments have been somewhat equivocal. Thus Macleod[30] states that "There can be no doubt that insulin causes a rapid reduction in the amount of glycogen in the liver," but he also remarks later that at some stage after the blood sugar has become reduced by insulin, "The glycogenolytic process in the liver is stimulated." A similar suggestion was offered by Dudley and Marrian. In our third proposition we intimated that a factor does not have opposed functions with reference to the equilibrium which it protects. If we keep that idea in mind and remember that hypoglycemia calls forth sympathico-adrenal service, the results above detailed can be reasonably explained. It is significant that in the experiments of McCormick and Macleod, despite an effort to give doses of insulin "just insufficient to cause convulsions," convulsions occurred in 6 out of 15 cases; in the experiments of Dudley and Marrian the animals were killed on the appearance of convulsions; in the experiments of Babkin, though "convulsions were not observed," the glycemic percentage was far below the critical level. In all these experiments, therefore, the conditions were such that the hepatic glycogen stores were being drawn upon, not by direct action of insulin, but by the direct action of the factor opposed to insulin—the sympathico-adrenal factor—made to operate powerfully by the insulin hypoglycemia. This conclusion is supported by the testimony by Burn[31] that a small dose of insulin, mildly effective in the normal animal, causes in an animal treated with ergotamin profound hypoglycemia, with convulsions and collapse; for ergotamin, though having no influence on the action of insulin, paralyzes the protective sympathico-adrenal reaction. That the secreted adrenin plays an important part in this reaction is proved by the fact that the fall of the glycemic percentage is not checked, or is only slightly checked, at the critical point, if the adrenals have previously been inactivated,[5] and also under such conditions by the appearance of convulsions sooner and after smaller doses of insulin than in animals with active glands—a phenomenon observed by Sundberg,[32] by Lewis[33] and by us.[5]

From all the foregoing evidence it appears that the normal level of blood sugar is preserved by the sympathico-adrenal factor acting on the low side of the equilibrium and by the pancreatic factor and the renal overflow acting on the high side. Much still remains to be learned regarding the conditions bringing the islands of Langerhans into play. From the experiments of Banting and Gairns,[34] the inference may be drawn that a nervous control of insulin secretion is not necessary. That does not prove, however, that nervous control does not exist and could not be useful—the innervation of the heart is not *necessary!* The observations of De Corral[35] and of

McCormick, Macleod and O'Brien[36] point to vagus impulses as causing a discharge of insulin into the blood stream. Recent (unpublished) studies by Britton at the Harvard Physiological Laboratory, as well as the investigations of Clark,[37] have corroborated the earlier evidence. In harmony with these results are those announced by Lewis and Magenta,[38] that after section of the abdominal vagi a given dose of insulin is less effective than before. Because in the presence of high glycemic percentages remnants of the pancreas degenerate,[39] and the islet cells show signs of overwork,[40] it seems probable that just as the adrenals are stimulated by hypoglycemia, so likewise the "islands" are stimulated by hyperglycemia, that is, that each secretion is involved in a righting response which restores the normal equilibrium. If further research proves that the vagus provides a fine adjustment for insulin secretion, as the sympathetic does for adrenal secretion, it will be peculiarly interesting because of the common opposition between vagal and sympathetic functions.

A caution appears to be necessary here lest the ideas just expressed be taken as confirming Zuelzer's theory of the adrenal origin of diabetes. Indeed, Stewart[42] has declared that my interpretation of the sympathico-adrenal service in maintaining the normal glycemic concentration is only an elaboration of that theory. The essence of Zuelzer's theory was that the adrenals and the pancreas are such aggressive antagonists that when the pancreas is removed diabetes follows because of the unchecked action of the adrenals. The theory has no sound basis. And our observations, that sympathico-adrenal activity, roused by hypoglycemia, is promptly checked by hyperglycemia and that it is made to work again only when the blood sugar has *fallen* well below the usual level, should have prevented anybody from imagining that our experiments in any sense support Zuelzer's idea. Instead, they raise the question whether the high sugar level of diabetes may not be associated with a depression of sympathico-adrenal function.

It will be recalled that in our fifth proposition we suggested that when opposed factors assure an equilibrium there may be more than one on either side. Indeed, a primary action of the islands of Langerhans and the coöperative overflow arrangement in the kidneys may be regarded as a double device preventing a rise in the glycemic level. On the other arm of the balance may be placed the testimony of Olmsted and Logan,[20] that the pituitary body is important. They state that typical convulsive seizures occur in decerebrate animals if the pituitary body has been removed, but that otherwise even massive doses of insulin fail to lower blood sugar to a marked degree. This result has been associated with the observation by Burn,[31] that pituitrin can lessen or entirely prevent insulin hypoglycemia. The conclusion that the posterior lobe of the pituitary may collaborate with the adrenal medulla thus

seems justified. In a recent investigation, however, Bulatao and I[43] have shown that in decorticated animals with intact pituitary glands insulin regularly causes a drop in the glycemic concentration, and we have called attention to the same phenomenon in three similar cases described by Olmsted and Logan. Furthermore, we showed that in decorticated and decerebrated animals sympathico-adrenal activity may be maximal and may therefore retard or lessen the effect of insulin. For Olmsted and Logan to conclude on the basis of their few cases, which are not decisive, that the high blood sugar after decerebration is maintained by pituitary influence, seems to us unwarranted. In other words, though pituitrin as a pharmacodynamic agent inhibits the action of insulin, proof is still lacking that a pituitary secretion as such has that effect, and could coöperate with adrenal secretion.

Because of the effects which hypothyroidism, hyperthyroidism and thyroid feeding have in disturbing the glycogen content of the liver and influencing sugar tolerance,[44] and also because of reported hypersensitiveness of thyroidectomized animals to insulin,[45] it may be that the thyroid normally collaborates with the sympathico-adrenal apparatus. The evidence on this point is still too vague and uncertain, however, to justify discussion of it in this paper.

In our fourth proposition we mentioned that factors opposed in one region of the body may be collaborators in another region. This is perhaps the case with adrenin and insulin. They are opposed with respect to glycogen storage in the liver. They may be collaborators, however, in the utilization of sugar in muscles. Various investigators have found that injected adrenalin accelerates metabolism,[46] and recent Harvard studies have proved that secreted adrenin has the same effect,[47] and that the effect occurs when the circulation is almost wholly confined to muscles (not yet published). Adrenin causes in the isolated heart not only a greater consumption of oxygen per unit of time but also may cause total disappearance of the stored glycogen.[48] Hepburn and Latchford[49] observed that insulin accelerates removal of glucose from the perfusing fluid by the isolated mammalian heart, and Burn and Dale[50] noted that insulin causes rapid removal of glucose in a decapitated and eviscerated preparation, that is, when the heart and skeletal muscles are the only important metabolizing organs. The early stages of insulin action in such a preparation are characterized by increased oxygen consumption, with a respiratory quotient of unity. Thus insulin and adrenin, antagonists in the liver, appear to be collaborators elsewhere. Insulin may promote everywhere the passage of sugar from the blood into cells. In muscle cells adrenal secretion may work with insulin to facilitate the chemical changes underlying contraction. All this, however, remains to be proved. The suggestion is mentioned

here merely to illustrate the possibility of different relations of physiologic agents at different places in the organism.

Some Hints at Factors Affecting Protein Equilibria. Protein is quite as important as carbohydrate for bodily welfare and function. It is necessary for such invaluable services as building the cellular structure of the organism, repairing or restoring the worn or wasted parts, and providing the essentials for coagulation and for normal composition of the blood. It is constantly being disintegrated and lost from the body, and the possibility of securing a new supply is not always at hand. Since there is an elaborate arrangement for storing excess of carbohydrate and for liberating it as required, it would appear reasonable to look for a similar arrangement for storing indispensable protein against a time of need. The process of deaminization and the excretion of extra nitrogen indicate that accumulation of protein must be limited. The existence of a nitrogen equilibrium, capable of being altered and adapted to the requirements of the organism, implies that there prevails an orderly regulation for riddance or retention and the maintenance of a steady state.

The reality of a reserve or "deposit" protein has often been debated. Gradually there has developed a considerable body of evidence that with abundant protein feeding the hepatic cells can store protein just as they can store glycogen. More than forty years ago Afanassiew[51] noted that if "albuminates" were fed to dogs the liver became firm and resistant, and the hepatic cells increased in size and contained between their protoplasmic strands many fine sharply outlined granules, protein in nature. Seitz[52] brought further support, finding that in fed animals the total nitrogen of the liver in relation to that of the rest of the body was from two to three times as great as in fasting animals. The observations of Berg[53] have been especially significant. In 1914 he reported that in the hepatic cells of animals which are given protein there appear numerous small droplets or masses which are clearly distinguishable from the cell structure, which react as protein to Millon's reagent, which are caused to disappear by fasting, and which are restored only when protein or amino acids are fed. In 1922 he showed that these droplets can be distinguished in fresh teased-out liver cells stained with neutral red, and that they give the ninhydrin reaction of the simpler proteins. Berg's earlier observations have been fully confirmed by Stübel[54] and by Noel.[55] This histologic evidence for a protein reserve has been corroborated by Tichmeneff's chemical studies.[56] He starved mice for two days, then killed half of them and after giving the others an abundance of cooked meat killed them and compared the livers of the two groups. Expressed in percentage of body weight, the livers of the meat-fed animals had increased about 20 per cent, with the hepatic nitrogen content augmented between 53 and 78 per cent.

The concept of storage of valuable material involves the idea not of miserliness but of service—the appropriate use of the material outside the storage place. There appears to be at present no proof that protein is taken from the liver for use in another part of the body which requires restoration or improvement, though the possibility that such a transfer could occur would justify an attempt to search for it. There is testimony, however, to a function which the liver performs in maintaining the protein constituents of the blood. Kerr, Hurwitz and Whipple[57] found that after depletion of blood plasma (by bleedings and injections of washed blood corpuscles in Locke's solution) the restoration of the serum protein is delayed if the liver has been damaged or has been sidetracked by an Eck fistula. Furthermore, liver injury is associated with a fall in the serum proteins. Although in the blood of the normal animal fibrinogen is rapidly re-formed after being removed, Meek found that it fails to be re-formed if the liver is unable to act.[58] It seems, therefore, that the liver plays a fundamental role in the production of fibrinogen. In the production of antithrombin or antiprothrombin as well, and possibly of heparin also, there are indications that the liver is concerned and thereby might influence deeply the coagulation of the blood.

The serum proteins remain at a remarkably steady concentration, fluctuating only slightly with fasting, feeding, health or disease. And yet, as shown above, when they are reduced the liver soon restores them. Again the factors concerned with blood clotting are ordinarily in balance, so that coagulation takes a moderate and fairly uniform time. The relations can be disturbed, however, so that the time is longer or shorter. In experiments by Gray and myself[59] we obtained records of a shortening of the clotting time of blood by adrenalin injections if the blood is allowed to circulate through abdominal organs; the phenomenon fails if the circulation is confined above the diaphragm or if the intestines and liver have been removed. Increased adrenal secretion induced by splanchnic stimulation or excitement has a similar effect, as shown by experiments done in coöperation with Mendenhall.[60] According to Grabfield,[61] adrenalin increases the prothrombin element in the blood. It is significant that blood taken at the height of the hypoglycemic reaction, when sympathico-adrenal activity is maximal, "clots almost immediately it is withdrawn," as Macleod[30] has remarked, and as we also have noted. Finally, as Gray and Lunt[62] showed, a large hemorrhage hastens the coagulation of blood if the liver(and intestine) is in the circulation, but not if the blood flow is excluded from the abdomen. Since the sympathetic is stimulated by considerable hemorrhage, probably sympathico-adrenal action is normally involved in the response.

Additional evidence that the protein material of the liver can be called out by appropriate stimulation was furnished by Stübel,[54]

who found that the deposited droplets or small masses in the hepatic cells could be greatly reduced by injecting adrenalin subcutaneously. Moreover, in collaboration with Uridil and with Griffith,[63] we have shown that after protein feeding, stimulation of the nerves of the liver causes discharge of a still undetermined substance which accelerates the heart and causes a noteworthy increase of arterial pressure. The phenomenon is reduced to insignificance in animals which have been fasting, or which have been fed carbohydrate or fat.

From the foregoing observations we may conclude that the liver is an organ of central importance not only for carbohydrate, but also for protein metabolism. It shares with other parts the power of constructing protein from amino-acids, but when large amounts of protein are fed it lays by a reserve or deposit to a much greater degree than do the other parts.[56] This reserve can be called out by sympathetic stimulation and by adrenin. In maintaining the normal consistency and coagulability of the blood the liver is indispensable. Here are steady states in which the liver performs quite as important a task as it performs in the carbohydrate balance of the body, and probably the factors which control the situation act with quite as great a degree of nicety. Unfortunately we are still in a twilight zone which surrounds the problem, and vision is not clear. Hints have been given as to factors affecting the protein levels, but much work must still be done before we shall be well informed regarding them or their ways of producing steady states.

An Endocrine Factor Operating to Maintain the Temperature Equilibrium. The uniform temperature of warm-blooded animals, though they are exposed to very different environmental temperatures, has already been alluded to as an outstanding example of physiologic constancy. The temperature equilibrium is maintained by opposing factors. Concerning the nature of the physical factors, vasodilatation and sweating, which operate when the body temperature tends to rise, there has been no difference of opinion. On the other hand, factors which are set in action when the temperature tends to fall have been the subject of discussion for more than a third of a century. Speck,[64] Loewy,[65] Johansson[66] and Sjöström[67] have concluded from experiments in which subjects were exposed to cold surroundings that the increased metabolism which results is to be explained wholly in terms of shivering or other muscular contraction. Voit,[68] Rubner[69] and recently Leonard Hill and his co-workers,[70] on the contrary, have conducted experiments in which subjects were similarly exposed to cold surroundings, but usually for long periods, and have found acceleration of the metabolic rate with no demonstrable muscular movements. "It is incomprehensible," Rubner wrote, "that many physiologists can still doubt the presence of this powerful regulating mechanism. And it is just as

incomprehensible that the increase of heat in the presence of cold is ascribed solely to the gross shivering of the animal." What the nature of the chemical regulator is he did not suggest.

When warm-blooded animals are exposed to cold, the striking reactions are erection of hairs or ruffling of feathers, constriction of peripheral vessels and increase of blood sugar. These are signs that the sympathetic division of the autonomic system is in action. Is secretion from the adrenal medulla augmented under these conditions? The answer to this question has interesting bearings on the old controversy regarding chemical control of body temperature. Since 1906 various observers have found that adrenalin stimulates oxygen consumption in isolated organs or in the body as a whole. This pharmacologic evidence was given a physiologic significance when Aub, Forman and Bright,[71] at the Harvard Physiological Laboratory, found that if the adrenal glands are removed, though blood pressure and the body temperature remain unchanged, the metabolic rate may drop as much as 25 per cent below the previous normal level, and when later McIver and Bright[47] demonstrated that increased adrenal secretion accelerates the oxidative processes of the body. Clearly, if cold excites a greater ourpouring of adrenin into the blood stream it would induce a faster burning in the body just when there would be need for it.

Cramer[72] and Fujii[73] have reported reduction of the chromaffin substance of the adrenal medulla in animals exposed to low temperatures, but that condition, as Trendelenburg[74] has suggested, may not have resulted from overdischarge but from underproduction. More direct evidence of an increased medulliadrenal secretion brought on by cooling was obtained by Hartman and his collaborators.[75] Using the completely denervated iris of the cat to signal greater discharge of adrenin, they observed that dilatation of the pupil resulted when the cats were dipped in cold water or when they were dipped in warm water, and while wet were placed in a cold room or exposed to a current of cool air. The dilatation failed to occur if the adrenal glands were removed or inactivated. The use of the iris by Hartman has been severely criticized by Stewart and Rogoff,[76] who, however, have not used the completely denervated structure themselves. They have, therefore, no good basis for judgment. Because Hartman's results have been doubted, and also because we desired to eliminate quite certainly any emotional element (which wetting may have roused in the cat), Querido and I[77] have investigated the reaction by other methods.

As in other experiments, we have employed the denervated heart as an indicator of augmented adrenal secretion. We tried several different modes of exposing animals to cold before we hit upon the one which proved most satisfactory—that of introducing into the stomach a known amount of ice-cold water. The body heat of the animal passes into the cold fluid, and, unless the temperature is

to fall, heat production must be increased to compensate for the loss. We have called the situation confronting the organism under the circumstances its "heat liability." Obviously, since the weight, the temperature and the specific heat of the water are known, the number of calories which the animal must conserve or produce, or both, in order to prevent a temperature fall, can be calculated and nicely adjusted to the purposes of the experiment.

When heat liabilities varying between 1050 and 2400 small calories per kilogram were established there were invariably faster rates of the denervated heart, ranging from 15 to 64 per cent increase. When the adrenal glands were inactivated, and similar heat liabilities were presented to the organism, the increases ranged between 2 and 6 per cent only. And if, instead of ice-cold water, water near the body temperature was used the percentage increase was negligible. Since cold slows the rate of the isolated heart, the faster rate which follows the introduction of cold water occurs in spite of adverse conditions, a true physiologic response. And since this response fails when the adrenal glands are not acting, the inference is justified that the faster heart rate is a consequence of greater adrenal secretion.

If the heat liability is more than 1000 calories per kilogram acceleration of the denervated heart is almost uniformly attended by shivering. Thus, two calorigenic factors, secreted adrenin and muscular movements, are coöperating to protect against a shift of the temperature equilibrium toward the low side. But the shivering factor is not an essential part of the reaction, for if a heat liability of only 900 calories per kilogram is to be met shivering rarely occurs; if it occurs it is of short duration. The heart rate is faster, however, showing that the adrenal factor is operating.

The increase of adrenal secretion when the organism is exposed to the danger of too rapid heat loss, and the ability of naturally secreted adrenin to accelerate heat production, point to a physiologic reaction the services of which to the organism ought to be demonstrable. To test the capacity of this reaction we have studied the effect of a certain heat liability on shivering when the adrenal glands were active or inactive, and we have observed the influence of heat liability on the metabolic rate in the absence of shivering.

I have already remarked that if a heat liability of 900 calories is presented to the organism (cat) shivering rarely occurs or is brief. In 15 cases shivering occurred only twice and lasted in each instance only three minutes. In 15 cases in which the adrenals were inactivated by removal of one gland and denervation of the other the same heat liability per kilogram caused shivering in 13, and furthermore the shivering usually lasted considerably longer than in the control series—for six, seven, eight, eleven, thirteen and even sixteen and seventeen minutes instead of three minutes.

Thus the primary protection against a heat deficit in the body is found in activities of the sympathetic system (erection of hairs, vasoconstriction, liberation of easily combustible sugar and discharge of adrenin), for these responses occur before shivering occurs and may be the only manifestation of the influence of a heat liability. If animals have been deprived of the calorigenic service of the adrenal medulla, however, greater demands are made on muscular activity as a means of maintaining the normal temperature. Under normal conditions, therefore, two lines of defense are erected against a shift of the temperature equilibrium toward the low side. The first line is the sympathico-adrenal mechanism; if that fails and the temperature tends to drop in spite of it, the second line, muscular action or shivering, is invoked to produce the needed heat. And just as the convulsive seizures in hypoglycemia are attended by a greater adrenal discharge, so likewise is shivering due to cold thus attended. In both circumstances the introduction of the muscular factors marks a climax of the action of the automatic arrangements for defense.

If the foregoing inferences are correct it should be possible to demonstrate a faster metabolic rate in response to a bodily need for heat, quite apart from any muscular quiverings or contractions. To secure evidence on this point Querido and I, and later Bright, Britton and I, have studied the change in the metabolic rate in human beings when a known heat liability was created by taking ice-cold water or that combined with ice. We have now 19 satisfactory observations on 12 different subjects. The heat liability ranged from 360 to 512 small calories per kilogram. The metabolic rate has increased in these cases as much as 35 per cent, though the usual increase was not more than 17 per cent, and this without any sign of shivering either objective or subjective. Commonly the first effect of taking the cold water is a drop in metabolism, which is followed by the rise, which reaches its maximum at periods averaging twenty-five minutes after the liability was established.

The observations described above have direct bearing on the old controversy regarding the nature of the chemical agencies which help to preserve the temperature equilibrium of warm-blooded animals. Careful examination of the records of the experimenters who have argued that muscular contraction alone is the source of needed heat shows that they reported substantial increases of metabolism unattended by shivering. Furthermore, they failed to recognize that shivering may coëxist with and effectively mask a true chemical calorigenesis. And finally they have inferred that because a chemical mechanism did not operate in certain short experiments the mechanism does not exist—an inference having slight value when confronted by good evidence to the contrary. The results of our experiments are definitely opposed to the idea

that a single factor, the muscular factor, is relied upon to keep the temperature balance from tipping downward. They bring support to the testimony and the argument of Voit and of Rubner, and offer an explanation of the chemical regulatory device which they postulated.

The evidence which has just been presented is not to be taken as excluding still other coöperating agencies. The fact that thyroid activity accelerates metabolism, that thyroid removal lowers the metabolic rate and renders one more sensitive to cold, that the thyroid gland is probably subject to sympathetic control,[78] that it enlarges in animals exposed to low temperature,[79] that in the compensatory hypertrophy of a remnant the evidences of hyperactivity are greater if the animal is exposed to frigid surroundings[80]—all these observations are highly significant of possible sympathico-thyroid collaboration in the upkeep of body temperature. As Aub[81] has suggested, the sympathico-adrenal service may be employed for quick action and the thyroid may act in the same direction, but for more enduring needs. But here we must have more facts before we are warranted in giving thyroid function definitely a place among the compensatory factors evoked by a threatened shift in the temperature equilibrium.

In the foregoing discussion I have used to a large extent the results obtained in personal investigations. This emphasis will not, I trust, be interpreted as implying an overvaluation of the subjects studied or of the results achieved. It seemed best to rely on first-hand experience rather than to summarize the work of others. Furthermore, I wished to illustrate the interest which is added to a search for new facts if certain general ideas are allowed to suggest the direction of the experimenter's imagination and his efforts at securing insight.

In stating the first of the six propositions, that is, that a steady condition in the body implies physiologic agencies serving to maintain it, I mentioned several types. The type of opposed agencies has been illustrated by the operation of the sympathico-adrenal and the probable vago-insular mechanisms in keeping normal the blood-sugar level, and also by the regulation of the temperature equilibrium by physical and endocrine factors. The outflow or escape type has been illustrated by the function of the kidneys when there is too great a rise in the glycemic percentage. Questions at once appear as to other constant metabolic states, such as the storage and disposal of nitrogen, the laying by of fat, and the constancy of the organic and mineral constituents of the blood. In all these equilibria what agents are at work to limit the variations? What types do they represent? Though there are hints of answers to these questions, reliable information must still be sought.

The second proposition, it will be recalled, postulated corrective activity whenever an equilibrium is disturbed. This service was rendered, as we have seen, by the sympathico-adrenal apparatus in the presence of both hypoglycæmia and hypothermia. If this second proposition is generally true, not only must we look for agents which protect a steady state from serious disturbance, but also we must search for the control which makes them act with greater vigor, the more serious the disturbance. Related to this adjusted response is the fifth proposition: That accessory protective functions may be expected to coöperate if the primary functions fail. We have seen this situation in the coöperative activity of the kidney and the pancreas in resisting hyperglycæmia, we have seen it also in the vasoconstriction, the increased adrenal secretion and the shivering which constitute progressively the three lines of defence against a drop in the temperature level of the body. We should keep our minds alert, therefore, not only for regulators of steady states but for the government of the regulators, and for the combination of regulators working toward the same end.

A general inquiry, important for clear understanding of body organization, would be one directed toward determining, so far as possible, the primary or immediate agencies, as contrasted with the secondary agencies, which induce a change of state. For example, we have seen that sympathico-adrenal stimulation is an immediate cause of glycogenolysis. Obviously any other condition inducing glycogenolysis may act, not directly on the liver, but through the sympathetic approach. Until the primary factors are known and properly recognized we are sure to have confusion—such confusion as is implied in the idea that a corrective agent operates in both directions at the same point.

In my opinion an attempt at present to develop an elaborate and intricate conception of the interrelations of the endocrine glands would be altogether premature and might be quite misleading. The necessary factors are not at hand. But the idea that endocrine factors play an important rôle in establishing and maintaining physiologic equilibria is reasonable and moderate in its scope, and does not involve a far-reaching projection of theory into the unknown. That the idea has value not only in raising questions regarding the existence and nature of balanced states but also in suggesting ways in which endocrine agencies may affect these states has, I hope, been made evident by the instances which I have cited.

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EFFECT OF ROENTGEN RAY IRRADIATION ON RED BLOOD CELL PRODUCTION IN CANCER AND LEUKEMIA.*

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Introduction. There are several views as to the nature of the action of Roentgen rays on living tissues. It is generally felt that small doses have a "stimulating" action, and that very large doses are "depressing." There is an intermediate dosage which frequently is noneffective in producing visible changes in living organisms. The "depressing" doses bring about their effects by causing the death of the tissue. Whether this destructive action is one of disturbed cell division, or whether it is corrosive, or whether it brings about its effects in some other way, is still a matter for investigation. Some light is thrown on this subject by observing the effects of Roentgen ray irradiation on the blood corpuscles of

* This paper, under the title of "On the Nature of the Action of Roentgen rays on Living Tissues," was awarded the 1925 Alvarenga Prize of the College of Physicians of Philadelphia.

This paper is No. 60 of a series of studies on metabolism from the Harvard Medical School and allied hospitals. Expenses of this investigation have been defrayed, in part, by a grant from the Proctor Fund of the Harvard Medical School for the study of chronic diseases.

patients with leukemia or with cancer. The blood corpuscles offer especially suitable material for this investigation. The white blood cells may be recognized in the peripheral circulation from the myeloblast stage to the adult polymorphonuclear leukocytes. Of the red cells, the normoblast, the reticulocyte, the granule red cell and the adult red corpuscles may be recognized (Fig. 1). The granule red cells[1] are corpuscles which appear mature but contain, as their only differentiated internal structure, a refractive granule 0.5 micron in diameter. They represent a late stage in the maturation of the red corpuscle, and constitute about 1 per cent of the circulating red corpuscles in health. Changes in the percentage of reticulocytes and granule-red corpuscles can be observed during the course of a few hours after Roentgen ray therapy. The results can be interpreted numerically in terms of increased or decreased maturity. The effects of irradiation on the red blood corpuscles are found to be very definite when studied by this method.

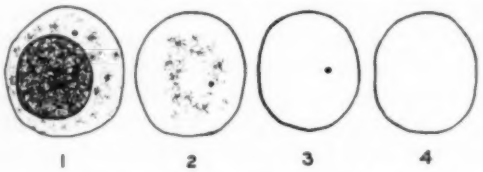

FIG. 1.—Four stages in the maturation of the red blood corpuscle, supravitally stained. (1) Normoblast; (2) reticulocyte; (3) granule red blood cell; (4) mature erythrocyte. The reticulocyte and the granule red blood cell are the two forms considered in studying the effects of irradiation in this paper.

Variations in Percentage of Young Red Blood Corpuscles. In order to evaluate the changes in the percentages of reticulated and granule red blood corpuscles after irradiation it is necessary to appreciate clearly the normal variations. In health, while the numbers of these corpuscles in the peripheral blood vary around 1 per cent, increases to 2 or 3 per cent may take place without evidence of disease. An increase above 3 per cent usually means an abnormal rate of blood production, and each degree of increase above this is of much more pathological significance than the variation below 3 per cent. The bone marrow appears to be "set" at a level of reticulated or granule corpuscle production with a physiological leaway of 1 to 3 per cent. Once the maximum is exceeded, small increments (1 per cent) are definitely significant. Thus a change from a total count of 1 per cent to a total count of 2 per cent has little pathological significance; whereas a change from a total count of 6 to 7 per cent has a much greater pathological import.

Previous Work on the Effect of Irradiation on Red Blood Corpuscles. Various observers have described changes in the number or the kind of red blood corpuscles after Roentgen ray or radium irradiation.

The data are not comparable because of the differences in dosage and technic.

Heineke[2] noted a late decrease in the number of erythrocytes after irradiation. Aubertin and Beaujard[3] described a decrease in the number of erythrocytes in irradiated rabbits with an increase in the young forms (polychromatophilia, blasts). Morris[4] found no changes in the number or cytology of the red blood corpuscles immediately after irradiation of animals. Weigeldt,[5] noticing the increase in the percentage of reticulocytes after irradiation, considered that the therapy had acted as an irritant to the bone marrow. Strumia[6] described the effect of radium placed over the extremities of a patient with myelogenous leukemia. He noted an increase in the number of nucleated red cells and other immature red blood corpuscles in the peripheral circulation during the week after the first application of radium, with a decrease after the subsequent treatments. The increase in the more immature forms during the initial period he considered as an evidence of bone-marrow stimulation. Millet and Mueller[7] recorded a considerable fluctuation of the number of red blood cells, with a definite increase in the count at some period within the first three days after irradiation of cases of squamous cell carcinoma of the cervix uteri and vagina with radium. Minot and Spurling[8] have reviewed the literature and from direct observations they conclude that there is no distinct or constant variation in the number or no specific change in the cytology of the red blood corpuscles during the course of days or weeks after therapeutic irradiation.

Material and Methods.—Blood for examination before and after Roentgen ray irradiation was obtained from 30 patients during the course of their clinical study. The cases included carcinoma of the breast, 6; of the uterus, 7; of the prostate, rectum, pancreas and stomach, 1 each; Hodgkin's disease, 2; chronic myelogenous leukemia, 7; chronic lymphatic leukemia, 1; erythremia, 2; chronic hemolytic jaundice, 1. Isolated observations were made on many other patients receiving Roentgen ray irradiation. Blood films were made on cover-glasses and stained supravitally with brilliant cresyl blue, with Wright's stain as a counterstain. Differential counts of 1000 to 5000 red blood corpuscles were made, representing from 30 to 150 or more microscope fields in different parts of the films. Hemoglobin determinations were made by the Sahli method. Wherever possible the blood was collected at the same time of the day and in the same relation to meals, and while the patients were at rest. The capillary blood from the ear was used. The total red blood corpuscle and leukocyte counts and the hemoglobin determinations were made by several persons, and must be interpreted with this in mind. All the reticulated and granule red cell counts were made by the author.

The irradiation was applied over the region of the neoplasm

or the spleen, lymph glands, or long bones. The number of electrostatic unit seconds and the area of exposure are given with each case discussed. The high voltage (170 kv.) constant potential short wave-length Roentgen ray described by Duane[9] was used. There was usually an average daily dose of about 600 electrostatic unit seconds (corresponding under these conditions to one-half erythema dose) exclusive of secondary irradiation, repeated on two to four successive days. The distance was 80 cm. in each exposure, and 0.5 cm. thickness of copper was used as a filter. The average effective wave length was from 0.170 A to 0.185 A degrees.

Data. The following are a few of the cases selected to illustrate the general principles shown by all the cases. Taking the changes in the percentage of granule red blood corpuscles as the criterion, the cases fall into three general groups. The first group comprises cases in which the granule red blood corpuscles increased in percentage during the Roentgen ray exposure, and remained above the preirradiation level for more than a day. A second group includes cases in which the increase in the percentage of granule red blood corpuscles was very transient, with a decrease to the pre-irradiation percentage or below by the following day. A third group is made up of those cases in which the rise in the percentage of granule red blood corpuscles was either absent or so transient that it was not detected, with an occasional decrease in the percentage below the pre-irradiation level.

TABLE I.—CARCINOMA OF THE BREAST.

Day.	Roentgen ray E.S.U. Sec.	Granule red blood cells, per cent.	Red blood cells (millions per cu. mm.)	Hemoglobin, per cent.	Color index.	Leukocytes (thousands per cu. mm.)
1	....	2.5	5.9	89	0.75	9.8
2	....	2.2				
2	617	Portal 20 x 20 cm. Right breast, axilla, chest, anteriorly.				
3	....	4.3	4.7	92	0.97	11.0
4	....	4.0	4.5	94	1.00	8.0
5	....	3.2	4.8	96	1.00	7.8
7	....	2.4	5.6	....	....	9.6

Case Reports. CASE I.—*Carcinoma of the Breast.* A woman, aged fifty-one years. After a single exposure to the short wave-length Roentgen ray irradiation (Table I) there was both a relative and an absolute increase in the number of granule red cells, from 147,500 to 202,100 per cubic millimeter. The number gradually decreased and returned to the original percentage five days after the original treatment. There was a definite local improvement of the breast region clinically for four to six months. Later the processes became aggravated, and there was less response to treatment. Metastases appeared, and death followed in one year. No

leukopenia developed after this first irradiation. There was a slight decrease in the red blood cell count during the two days following the treatment, with a slight rise in the color index.

CASE II.—*Carcinoma of the Breast, Recurrent.* A woman, aged fifty-five years. The day following the first irradiation over the chest and mediastinum (Table II) the granule red cells had increased from 1 to 7.2 per cent, or an actual increase of from 60,000 to 388,800 per cubic millimeter. The next day the percentage had fallen to about its pre-irradiation level, and repeated treatments caused but a slight increase. The clinical results in this case were poor. It is not known whether leukopenia developed, as no further leukocyte counts were obtainable. There was a definite rise in the color index after irradiation, with a decrease in the red blood cell count.

TABLE II.—CARCINOMA OF THE BREAST.

Day.	Roentgen ray E.S.U. Sec.	Granule red blood cells, per cent.	Red blood cells (millions per cu. mm.)	Hemoglobin, per cent.	Color index.	Leukocytes (thousands per cu. mm.)
1	600[1]	1.0	6.0	103	0.86	8.1
2	600[2]	7.2	5.4	110	1.02	9.2
3	500[1]	1.1	4.6	104	1.13	8.5
4	500[2]					
5	....	2.8	4.4	106	1.20	8.1
13	....	0.8	4.9	111	1.13	9.4

[1] Portal 20 x 20 cm. Chest, anteriorly. Given after blood counts were made.
[2] Portal 20 x 20 cm. Chest, posteriorly. Given after blood counts were made.

TABLE III.—CARCINOMA OF THE PROSTATE.

Day.	Roentgen ray, E.S.U. Sec.	Granule red blood cells, per cent.	Reticulocytes, per cent.
1	Before treatment[1]	2.6	2.2
1	500 portal 25 x 25 cm. Pelvis, posteriorly		
1	10 minutes after treatment	7.7	2.8
2	500 pelvis, anteriorly (after blood examination)	1.2	7.8
3	500 pelvis, posteriorly (before blood examination)	4.6	7.3

[1] Red blood cells, 2.7 millions per cu. mm.; hemoglobin, 60 per cent; leukocytes, 4700 per cu. mm.

CASE III.—*Carcinoma of the Prostate.* A man, aged seventy-five years. In contrast to the preceding individual, this patient had a marked anemia. There was a rapid increase in the percentage of granule red cells (Table III) noted ten minutes after the initial exposure, and a decrease in the percentage of reticulocytes. With the subsequent decrease in the percentage of granule red cells on

the following day, the percentage of reticulocytes increased and was sustained after subsequent treatments. The clinical results in this case were poor. A leukopenia was present in this patient before irradiation.

CASE IV.—*Carcinoma of the Rectum.* A man, aged sixty years. As shown in Table IV, irradiation was followed by very slight changes in the number of granule or reticulated red blood cells. There was a fair but temporary improvement in the rectal condition.

TABLE IV.—CARCINOMA OF THE RECTUM.

Day.	Roentgen ray, E.S.U. Sec.	Granule red blood cells, per cent.	Reticulocytes, per cent.
1	.....	2.0	0.2[1]
2	.....	2.3	0.5
2	500 pelvis, posteriorly portal 20 x 20 cm.		
2	1 hour later	0.9	0.3
2	4 hours later	2.6	1.2
3	500 pelvis anteriorly portal 25 x 25 cm.[2]		
3	First 30 minutes of exposure	0.8	1.4
3	2 minutes after total exposure	0.9	0.6
3	4.5 hours after treatment	0.9	0.7
4	500 pelvis, posteriorly portal 25 x 25 cm.		
4	1 hour after	1.4	1.3

[1] Leukocytes, 11,400 per cu. mm.; hemoglobin, 75 per cent.
[2] Red blood corpuscles 5.73 millions per cu. mm.; hemoglobin 93 per cent; leukocytes, 15,000 per cu. mm.

TABLE V.—CARCINOMA OF THE STOMACH.

Day.	Roentgen ray E.S.U. Sec.	Granule red blood cells, per cent.	Red blood cells (millions per cu. mm.)	Hemoglobin, per cent.	Color index.	Leukocytes (thousands per cu. mm.)
1	....	1.5	4.3	68	0.79	20.0
1	500[1]					
2	....	0.6	4.4	77	0.86	21.0
2	500[1]					
4	....	2.1	3.8	68	0.89	17.0
22	....	0.6	5.2	77	0.74	15.0

[1] Portal 20 x 20 cm. Epigastrium.

CASE V.—*Carcinoma of the Stomach.* A man, aged fifty-six years. On the day following the first treatment (Table V) the relative and actual number of granule red cells decreased, without significant change after a second treatment. These changes were within the limits of normal variations. The color index rose very slightly after the treatment with a decrease in the red blood cell count. Eighteen days later the red cell count had risen with a

decrease in the color index, although the variations were not marked enough to be significant. There was an apparent temporary improvement of the symptoms. Death followed thirty-three days after the last treatment.

CASE VI.—*Chronic Myelogenous Leukemia.* A man, aged sixty-eight years. After heavy doses of short wave-length Roentgen ray irradiation, the percentage of granule red cells (Table VI) was increased, and there was marked clinical improvement. After the exposure to radium there was but little change in the percentage of granule red cells, and no clinical improvement. The "control" period, covering the first eighteen days, without irradiation shows the fairly constant percentage within the limits of normal of granule red cells from day to day. The changes in the percentage of granule red cells preceded the changes in the immature white cells by twenty-four to forty-eight hours. After the Roentgen ray irradiations there was a rise in the color index without much change in the red blood cell count.

TABLE VI.—CHRONIC MYELOGENOUS LEUKEMIA.

Day.	Irradiation.	Granule red blood cells, per cent.	Red blood cells (millions per cu.mm.)	Hemoglobin, per cent.	Color index.	Leukocytes (thousands per cu .mm.)	Immature leukocytes per cent.
1	.....	1.7	2.9	35	0.60	123.0	31
9	.....	0.4	3.1	48	0.77	92.0	34
10	.....	0.9	3.5	49	0.70	131.0	40
18	.....	0.2	2.8	61	1.09	93.0	33
18	X 900 E.S.U. Sec.[1]						
19	.....	3.0	3.2	59	0.92	101.0	33
20	.....	...	3.3	67	1.02	63.0	10
32	.....	6.0	3.8	76	1.00	15.0	7
39	.....	2.2	...	..	....	.....	3
46	.....	3.2	...	..	....	.....	4
	(80 day interval)						
106	.....	1.9	4.6	90	0.98	51.0	20
119	.....	...	4.6	93	1.01	52.0	19
119	Rad. 5000 m.c.h.[2]						
121	.....	1.4					
	(85 day interval)						
206	.....	0.4	3.4	59	0.87	190.0	36
207	X 600 E.S.U. Sec.[3]						
208	.....	2.8	4.1	70	0.85	199.0	14
208	X 600 E.S.U. Sec.[4]						
208	X 500 E.S.U. Sec.[5]						
209	X 500 E.S.U. Sec.[6]						
210	.....	3.3	4.1	84	1.02	92.0	16
351	.....	0.7	3.8	65	0.86	110.0	38

[1] 20 x 21 cm. Spleen, anteriorly.
[2] Steel tube, 2 mm. lead, 2.5 mm. gauze, 6 cm. air. Spleen anteriorly.
[3] Portal 15 x 20 cm. Spleen, anteriorly.
[4] Portal 18 x 20 cm. Spleen, posteriorly.
[5] Portal 15 x 16 cm. Spleen, anteriorly.
[6] Portal 15 x 16 cm. Spleen, posteriorly.

CASE VII.—*Chronic Myelogenous Leukemia.* A woman, aged forty-four years. Irradiation over the spleen was followed by an appreciable increase in the percentage of granule red blood cells, with a rapid return to the pre-irradiation level with the cessation of the treatment. During the course of the next forty days a severe leukopenia developed, with marked anemia. During this time the clinical condition was very poor and the advisability of a blood transfusion was discussed. However, the number of reticulocytes was elevated, and the number of granule red cells was increasing. This was interpreted as a tendency for more red cells to reach a stage nearer maturity, and it was predicted that an increased production of mature white cells would follow later, as the processes in red cells appear to be more rapid than those in the leukocyte formation. Transfusion was postponed and Table VII shows the subsequent recovery. It will be noted that on the day following the first irradiation, the color index was increased, while on the day after the second and third irradiations there was a decrease. Fifteen days after the last irradiation the color index had begun to rise and continued to increase during the next month. During this period there was a gradual slight decrease in the total number of red blood corpuscles.

TABLE VII.—CHRONIC MYELOGENOUS LEUKEMIA.

Day.	Roentgen ray E.S.U. Sec.	Granule red blood cells, per cent.	Reticulocytes, per cent.	Red blood cells (millions per cu. mm.)	Hemoglobin, per cent.	Color index.	Leukocytes (thousands per cu. mm.)	Immature leukocytes per cent.
1	.....	1.5	...	3.6	58	0.80	265.0	29.0
18	.....	1.8	4.0	3.9	74	0.95	192.0	32.0
18	450[1]							
19	.....	3.9	1.1	3.4	72	1.06	124.0	7.0
21	500[2]							
22	.....	4.6	1.3	3.4	64	0.94	52.0	6.5
22	500[1]							
23	.....	1.4	2.9	3.8	68	0.89	41.0	4.0
38	.....	0.6	3.1	3.6	65	0.90	5.7	0.0
63	.....	1.3	5.9	2.4	50	1.04	1.4	0.0
66	.....	1.5	5.8	2.7	62	1.15	1.4	3.0
70	.....	2.7	4.1	2.1	60	1.43	1.7	2.0
84	.....	4.5	8.9	2.4	50	1.04	2.0	0.0
91	.....	5.4	5.3	3.0	69	1.15	6.2	2.0
98	.....	2.5	4.4	2.9	65	1.12	4.0	2.0
119	.....	...	...	4.3	82	0.95	8.4	1.0

[1] Portal 25 x 20 cm. Spleen, posteriorly.
[2] Portal 25 x 20 cm. Spleen, anteriorly.

CASE VIII.—*Chronic Lymphatic Leukemia.* A man, aged forty-nine years. After repeated exposures to radium this patient showed very little clinical improvement or change in the total or

differential leukocyte count, and very little change in the percentage of granule red blood cells. After two erythema doses of short wave-length Roentgen ray irradiation there was a marked change both clinically and in the blood. The increase in percentage in granule red cells was from 1.1 per cent before the irradiation to 6.3 per cent after it. This preceded the changes in the white blood cell count by twenty days. The difference in the action of the Roentgen rays and radium was probably a matter of dosage and not the result of any intrinsic differences of the two sources of radiation.

TABLE VIII.—HEMORRHAGE. CARCINOMA OF THE CERVIX OF UTERUS.

Day.	Roentgen ray, E.S.U. Sec.	Granule red blood cells, per cent.	Reticulocytes, per cent.	Red blood cells (millions per cu. mm.)	Hemoglobin, per cent.	Color index.	Leukocytes (thousands, per cu. mm.)
1	Hemorrhage[1]						
3	.....	5.0	3.3	3.6	55	0.76	10.0
4	.....	4.6	4.5				
5	.....	4.3	5.9				
6	.....	2.2	6.3				
7	.....	6.4	5.6				
8	.....	4.0	5.6				
9	.....	2.2	5.3	2.7	55	1.02	10.9
9	600[2]						
10	.....	1.6	5.2	3.4	55	0.81	11.0
10	600[3]						
11	.....	7.0	5.4				
11	500[2]						
12	.....	8.0	4.1	3.1			
12	500[3]						
12	10 min. after roentgen-ray	8.8	4.5				
13	.....	8.9	4.1				
14	.....	6.6	4.6	3.6	55	0.76	

[1] Severe hemorrhage from cervix of uterus for eight hours.
[2] Portal 20 x 20 cm. Pelvis posteriorly.
[3] Portal 25 x 25 cm. Pelvis anteriorly.

CASE IX.—*Hodgkin's Disease.*—A woman, aged twenty years. Short wave-length Roentgen ray irradiation failed to produce an appreciable change in the percentage of young cells during a period in which two transfusions failed to stimulate an increase in their number. During another period a transfusion was successful in increasing the number of granule red cells and an irradiation at this time had a similar effect. Two days after this irradiation the granule red cells decreased from 6.4 to 2.8 per cent, with a rise during this period in the percentage of reticulocytes, from 1.9 to 3.8 per cent. Before the irradiation the color index was 75 and the day after it was 103.

CASE X.—*Erythremia.* A woman, aged forty-four years. During the course of twenty-four hours after an erythema dose of short wave-length Roentgen ray irradiation over the long bones there was a slight but definite increase (from 3.3 to 4.5) in the number and percentage of the granule red cells. Six days later the percentage had decreased below the pre-irradiation number (1.9 per cent), and the percentage of reticulocytes had increased considerably (from 2.2 to 6.9 per cent). The color index before irradiation was 0.62. On the day after the treatment it was 0.72, and six days later it had risen to 1. In another case (male, aged forty years) there was an increase from 1.6 to 3.3 per cent in the number of granule red cells immediately after one short wave-length Roentgen ray irradiation treatment over the splenic region.

CASE XI.—*Carcinoma of the Cervix of the Uterus with Hemorrhage.* A woman, aged forty-eight years. After a severe hemorrhage from the cervix, the percentage of granule red cells was increased above normal (Table VIII), followed later by an increase in the percentage of reticulocytes. With the second Roentgen ray exposure the number of granule red cells increased from 1.6 to 7 per cent, reaching 8.9 per cent after the fourth treatment. It will be noted that while the percentage of granule red cells rose, the percentage of reticulocytes still remained above normal.

Discussion. The data from the preceding cases as well as those from the other cases studied, but not reported in this paper, were essentially similar. No gross differences in effects of Roentgen ray irradiation on the red blood corpuscles were associated with age (there were no young children in this series) or with sex. A single instance of a relation of temperature and granule red cell number was encountered in a case of chronic myelogenous leukemia, in which both the temperature (102° F.) and the granule red cell count which had been elevated for six days (3.1 to 5.1 per cent) suddenly fell to normal and remained so. The actual number of red blood corpuscles per cubic millimeter was not affected in as definite a manner as the number of leukocytes in any of the patients. The study of the cases, both those reported in the tables and others, shows that they may be divided into three groups on the basis of the changes in the numbers of granule red blood cells after irradiation. The first group includes those in which there was, after irradiation, an appreciable increase in the number and percentage of granule red blood cells which did not decrease to pre-irradiation level for a period longer than twenty-four hours (Cases I, VI, VIII and XI). The second group is made up of those in which the increase in the number and percentage of the granule red blood cells was present less than twenty-four hours before dropping to the pre-irradiation level (Cases II, VII and X). The third

group includes those in which the increase, if present at all, was so transient that under practical conditions it would be overlooked if the blood were not examined soon enough after irradiation was begun (Cases IV, V and IX). In some of the third group of cases no change may have taken place in the granule red cells at any time (Fig. 2). When classified according to the clinical course the cases fell into the same groups. In those patients in whom the rise of granules red blood corpuscles lasted at least two or more days the clinical results were good. In those cases in which no definite increase in the granule red blood corpuscles was noted after irradiation there was usually no clinical improvement in the irradi-

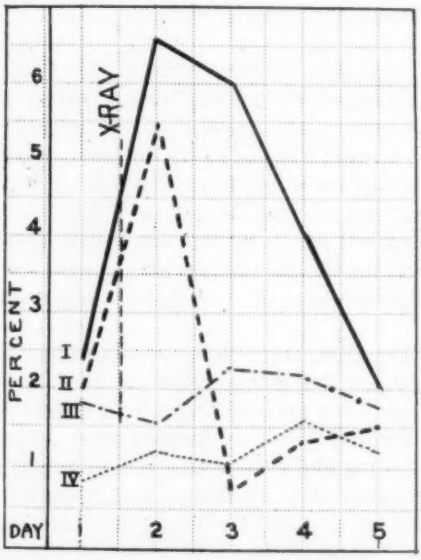

FIG. 2.—Diagram showing variation in percentage of granule red blood cells after Roentgen ray irradiation. I, II, and III are the three usual common types of change. IV, shows the variation in an untreated normal individual.

ated lesion. If the increase was temporary (twenty-four hours or less), and was followed soon by a decrease, the clinical results were those of too much irradiation, with a deleterious effect of varying duration on the patient's condition.

Source of Change in the Red Blood Corpuscles. The changes brought about in the red blood corpuscles appear to be the result of an effect on the cells and on the marrow rather than a change in the distribution of corpuscles in the circulating blood. Observations on Marathon runners[10] show that violent exercise with a consequent "stirring up" of the circulation did not appreciably change the percentage of young red cells, although the white cells

were definitely altered in number and kind. The changes in the blood cells following procedures calculated to "stir up" the circulation were studied by Drinker, Drinker, Kreutzmann[11] and by Schneider and Havens,[12] with the conclusion that changes in the volume or intensity of the circulation were not an adequate stimulus to dislodge immature blood corpuscles from non-hyperplastic bone marrow. However, differences in the percentage composition of the circulating leukocytes may be influenced by admitting into the circulation cells apparently dormant in the liver, spleen and other internal capillary areas. The percentage composition of the recognizable kinds of red cells does not appear to change proportionally. It seems, therefore, that the change in the number of young red corpuscles after irradiation is not one of redistribution of cells in different capillary areas.

The change after irradiation is very rapid, appearing in some cases after fifteen minutes of exposure. This takes place even without any significant change in the actual number of red blood corpuscles per cubic millimeter of the peripheral blood. At least any variation in the erythrocyte count is overshadowed by the normal percentage of error in counting red corpuscles. We have here an actual decrease or increase in the number of reticulocytes, with an increase or decrease in the number of granule red blood corpuscles. Some of the maturation changes may be brought about in the peripheral circulation and some in the bone marrow.

After the period of increased maturity of the red blood corpuscles a period of greater immaturity followed in some cases (Cases V, VII and X), with a rise in the number of reticulocytes. A similar change has been reported after intensive irradiation in the case of the white blood corpuscles[3] (Minot and Spurling,[8] p. 229). The change in the degree of maturity of the red cells and white cells corresponds to some extent to the reappearance of growth activity of irradiated cancer tissue, with the formation of multiple metastases, long after a radium or Roentgen ray treatment which has reduced the original focus to a quiescent state, the intermediate period varying with the type of tissue.

The increase in the number of reticulocytes which followed in some cases showed that the bone marrow must have been affected. The changes in the numbers and kinds of young red cells after irradiation with the short wave-length Roentgen ray indicates an apparent direct effect on the speed of the maturation processes. The first change after effective irradiation was an increase in percentage of the more mature red blood corpuscles, while the more immature decreased. This effect took place during irradiation, sometimes lasting for days, and at other times not much longer than the period of exposure.

The eventual increase in the number of red cells in many cases

of chronic myelogenous leukemia following irradiation treatment has been attributed to increased room in the bone marrow as the number of immature white cells decreased. The present observations, however, show that an additional factor is at work, as probably little change takes place in the number of white cells in the bone marrow during the first fifteen or thirty minutes of exposure of the body to irradiation. During this time the numbers of young red cells in the peripheral blood change markedly. The actual number of red cells per cubic millimeter may increase or decrease during the days immediately following irradiation. Within this period of time the change in number is seldom significant, rarely being more than 1,000,000 per cubic millimeter. Taking into account the fluid lost by the patient in vomiting and failure in some cases to replace it because of loss of appetite, and the inevitable loss of several pounds in weight during the period of treatment, the actual number of red cells per cubic millimeter of capillary blood gives little information as to the actual number of red corpuscles in the body.

Color Index. Although the total red cell count did not vary within significant limits immediately after irradiation, and frequently decreased temporarily during the week or two following, the color index rose in practically every case where the irradiation was effective, frequently increasing from less than 1 to 1 or more than 1. In 2 cases there was a fall in the color index immediately after the treatment. In both these cases a leukopenia developed in the following weeks (Case VII and one other of chronic myelogenous leukemia).

Relation to the Development of Leukopenia. Of those cases in which the data are complete, no leukopenia developed when the percentage of granule red blood corpuscles remained elevated for more than a day after irradiation. In Case VII the increase in number of granule red blood cells was definite after the first two exposures, but fell immediately after the third one. A leukopenia with 1400 white blood cells developed subsequently. If only one erythema dose had been given it is thought that sufficient irradiation would have been applied to produce the proper therapeutic result. Another case showed the wisdom of this procedure, so that when after one erythema dose the percentage of granule red cells began to decrease after having been elevated for less than two days after the second exposure, further treatment was suspended. Thus, while in some persons four exposures (two erythema doses, one anteriorly and one posteriorly) to the short wave-length Roentgen ray irradiation were necessary, in this second case the ideal results were produced by two.

Nature of the Irradiation Effect. The changes in the red cells from immature to mature suggest that a similar process may take place

in cancer tissue when it is irradiated. It seems more likely that the therapeutic irradiation effect is one of stimulation to go through the rest of the process of the life of the cell, reach maturity and die, rather than either of the alternate conceptions of a direct toxic or lethal action of the irradiation on the tissue.

The effect of the irradiation process is illustrated in Case XI, in which there was an increase in the number of granule red cells after irradiation during the period of regeneration after hemorrhage. From the point of view that this is an increase in the degree of maturation, the effect of Roentgen ray irradiation after hemorrhage is not detrimental. Watanabe and Harada,[13] considering only the reticulocytes and the nucleated red blood cells, naturally came to the opposite conclusion. They noticed the reduction in the number of reticulocytes and considered this as a depression of the bone marrow, following the usual interpretation, and advised against irradiation after hemorrhage.

Latent Period. Several phenomena after irradiation can be accounted for, if one takes the point of view that irradiation stimulates the cell to go through the rest of its life processes. Thus, there is always a "latent period" between the time of exposure and the time in which retrogressive effects are noted. It is the period in which the cell is becoming mature and reaches the height of its physiological development. When the cell becomes senile and approaches death the retrogressive effects are noted.

In the case of the red blood cells this period is extremely short. In the development of the white blood cells the process appears to be a little longer than in the red cells. With cancer tissue, as in carcinoma of the breast, no change may be noted in some cases for two weeks or longer. A histological study of irradiated cancer tissue shows that very little change takes place immediately. Double vital staining with neutral red and Janus green suggest that the cells go through a process very much like that of normal cells as they go through from youth to age. Thus Prigosen[14] has shown that the mitochondria decrease, while the neutral red-staining granules in the cancer cells increase in number during the periods succeeding irradiation, a process which can be interpreted from its analogy to the development of embryonic tissue as one of progress from youth to senility. The histology of therapeutic irradiation effects is not one of immediate necrosis. Nakahara[15] was able to find no microscopic evidence of direct injury of irradiation on tissues. This is also compatible with the observations described by Loeb[16] and others, of the comparatively greater resistance to irradiation of such mature tissues as adult muscles, ganglia and nerve fibers, over the more embryonic types. The resistance of birds' nucleated red blood corpuscles[17] is similar, as these cells are mature and are not analogous to the nucleated red

cells of man. Those cells which have already developed to maturity are more resistant, probably because the mechanism for development, division and differentiation can no longer be stimulated.

"Stimulating" and "Depressing" Doses. Small doses of Roentgen ray or radium irradiation are said to stimulate, and large doses depress. This has been described in connection with cancer tissues, plants and microörganisms. Bock[18] reported an increase in red blood cells after small doses, and decrease, with the appearance of immature forms in the circulation, after large doses. It is quite conceivable, however, that if a very slight stimulation were applied to growing cells, the cells would not necessarily be stimulated to complete their growth all the way to maturity, but would go on in their dividing process at a more rapid rate. The reproduction stage has usually been considered the critical one, although this is not necessarily true.[16] Alberti and Politzer,[19] on the basis of their experiments, conclude that, after irradiation, it is not the damage to the cells in the state of full mitosis which causes breaking down of the tissue, but it is the effect on the resting cells. The action, although not visible histologically at the time, is shown in a postponement of the cell division with more or less pathological mitosis which eventually leads to necrosis of the cells.

From the "increase maturation" point of view, all the effects of Roentgen ray irradiation are "stimulating." If irradiation is weak, the reproduction process continues but at a more rapid rate. If the stimulation is greater, the process of maturation goes on to completion, the rate and degree depending upon the strength of the stimulus. The cell passes the dividing stage, reaches maturity and dies. These effects of irradiation are what have usually been called the "stimulating" and "depressing" doses.

After the application of irradiation of certain intensities (greater than the stimulating dose but less than the depressing dose) to cancer tissue or to living organisms, no change may be apparent (Loeb,[16] p. 238). This seems to be true in those cases recorded here (Cases IV, V and IX) in which no effect was noted on the blood corpuscles or in the clinical condition of the lesion irradiated. The rate of stimulation under these circumstances apparently does not differ from the rate of stimulation affecting the body tissues at the time of the application of the irradiation. The young red blood corpuscles act similarly to the other tissues when the effective strength of the irradiation dose differs.

The Effect of Irradiation Not Specific. A study of the data brings out the fact that Roentgen ray irradiation does not cause any specific or peculiar change in the character or relative number of the red blood cells. All the variations are of a type that occur spontaneously in disease, with fever, with other types of therapy and with hemorrhage or transfusion. Sabin, Austrian, Cunningham

and Doan[20] noted that following transfusion there was first a slight increase in the degree of the maturity of young white cells in subacute myelocytic leukemia. Isaacs[21] had noted a similar change on the part of young red cells after blood transfusion, an effect very similar to that after irradiation therapy.

The increase in the degree of maturity of the red blood corpuscles in Case IX after some of the blood transfusions and after Roentgen ray irradiation during the same period, with the absence of effect of both agencies at other times, corresponds to the clinical reports of their effects on the red blood corpuscles of pernicious anemia patients. It is well known that a remission may be started sometimes after blood transfusion in pernicious anemia, but there are times when the course appears to be uninfluenced. Similar reports have been recorded after the use of Roentgen ray or radium irradiations over the spleen and long bones in this disease. Minot and Lee[22] noted beneficial results soon after Roentgen ray irradiation in 6 out of 10 patients. Bucky and Guggenheim[23] and Tomaner[24] had similar experiences, and other authors[25, 26, 27] report increases in the red blood cell count after irradiation of patients with secondary and aplastic anemia.

Irradiation stimulates in susceptible cases changes which are normal in the life of red cells, only the rate and time of initiation being changed. The same appears to be true of the effect of irradiation on leukocytes and on cancer cells. The maturation processes, once started, may continue long after the source of irradiation is removed, and death results from senility.

Summary and Conclusions. 1. Irradiation stimulates in susceptible cases changes which are normal in the life of a red blood corpuscle, the rate and time of initiation only being changed.

2. Effective short-wave Roentgen ray irradiation over any part of the body in man may be followed, in from one to twenty-four hours, by one of three responses of the young red blood cells. The granule red cells (corpuscles showing only a refractive granule) may show an appreciable and sustained increase in percentage, or the increase may be very transient or it may be negligible. Where there is an absolute or relative increase in the percentage of granule red cells there is frequently a decrease in the absolute and relative percentage of reticulocytes, unless the marrow is hyperplastic (hemorrhage).

3. Cases of cancer and leukemia, in which the increase in granule red corpuscles after irradiation is significant and sustained (two or more days), show a definite clinical improvement, and no leukopenia develops. In those cases in which there is no evident increase in the granule red corpuscles after irradiation, there is usually no clinical improvement in the irradiated lesion. If the increase is temporary (twenty-four hours or less), and is followed by an

abrupt decrease, the results are those of too much irradiation, a leukopenia develops, and the patient may become worse clinically.

4. In terms of degree of red cell maturity, clinically effective Roentgen ray irradiation causes an increase in the degree of maturity of the red corpuscles liberated into the peripheral circulation, starting during the period of exposure and lasting for from one to four days. This may be followed by an increase in some cases in the more immature red cells (reticulocytes).

5. The most frequent effect on the count per cubic millimeter of the red blood corpuscles in the peripheral circulation is a gradual temporary decrease, with an increase in the color index, which often becomes more than 1.

6. The change in the percentage of immature red corpuscles is one of orderly stimulation to reach maturity, through an effect on the cells themselves in the bone marrow and possibly in the blood stream. It takes place quickly, without an appreciable variation in the red blood cell count, and is different from the changes following redistribution of the cells in the peripheral vessels.

7. The percentage changes of the immature blood cells follow therapeutic irradiation over any region of the body, and appear to be a "systemic" effect of localized exposure.

8. The changes in the relative percentage of young red blood cells after therapeutic irradiation are similar to those taking place after blood transfusion.

9. The period between the application of the irradiation and the beginning of definite maturation changes in the red blood cells ("latest period") is probably a matter of minutes, as compared with hours or days for the leukocytes and weeks for carcinoma tissue.

10. Other points of similarity between the red blood cell changes after effective irradiation and those of cancer tissue are: (*a*) Development toward maturity and senility; (*b*) occasional period of immaturity subsequently; (*c*) so-called "stimulation" by weak doses and "depression" by large doses, with occasional absence of effect after irradiation of intermediate intensity.

11. From the evidence of the effect of irradiation on young red blood cells, all Roentgen ray irradiation may be considered as stimulative. Small doses may stimulate to division, large doses may stimulate to maturity and to death from senility, the rate for each tissue varying with its specific growth properties.

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ASSOCIATION OF DIABETES INSIPIDUS WITH OSTEITIS FIBROSA POLYCYSTICA.

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Neither diabetes insipidus nor generalized osteitis fibrosa polycystica is of frequent occurrence. In fact, the association of these diseases in a single patient has been observed so infrequently that the report of such a case appears to be justified.

Futcher[1] found 7 cases of diabetes insipidus recorded among the 403,535 admissions to Johns Hopkins Hospital from 1889 to 1904; among 370,000 admissions to the Mayo Clinic,[2] but 34 patients had diabetes insipidus. It was diagnosed as occurring in 17 of 35,492 patients treated in the medical clinic at Zürich[3] between the years 1867 and 1879. Gerhart[4] reported 55 cases recognized among 113,600 patients admitted to the Charité in Berlin during a period of twenty years. Thus, from a total of 900,000 hospital admissions, this disease was reported as occurring but 113 times. There is reason to believe that while diabetes insipidus is of rare occurrence in dispensary and private practice, it is, nevertheless, somewhat more common than is indicated by hospital statistics.

It is impossible to speak with accuracy as to the frequency of osteitis fibrosa polycystica. In 1910, Bloodgood[5] was able to collect from his own practice and from the literature but 12 cases of osteitis fibrosa, while Morton[6] writing in 1922, could tabulate but 63 cases of bone cysts of which 12 had been already included in Bloodgood's series. Of Morton's group, but 22 appear to have been cases of polycystic osteitis fibrosa. Schoen,[7] on the other hand, does not regard osteitis fibrosa as very rare.* This author has reported a case of degenerative bone disease associated with diabetes insipidus and corresponding more closely to the case which we are about to report than does any which we have found on record. Schoen[7] is of the opinion that osteitis fibrosa and Paget's disease cannot be differentiated one from the other. He bases this belief upon the following premises: (1) The pathological processes appear to be identical both in the gross and in histological structure; (2) clinical differentiation is, as a rule, impossible; (3) combination forms exist. Several hundred cases of Paget's disease have been described. Schoen[7] reports his case under the title of Osteitis Deformans (Paget) associated with Diabetes Insipidus and Nervous and Endocrine Disturbances. The existing confusion in nomenclature is thus made apparent.

* Two cases have been observed in the autopsy room of the Philadelphia General Hospital in the past five years. – Ed.

As to the excessive rarity of the association of diabetes insipidus with degenerative bone disease, there can be no doubt. A somewhat extensive search of the literature has enabled us to quote but 10 cases in addition to our own. These cases are as follows: (1) A group of 7 cases in each of which the syndrome of diabetes insipidus was associated with defects in membranous bones. Of these cases 3 were reported by Hand,[8] 2 by Schuller,[9] 1 by Christian,[10] and the last, in 1923, by Grosh and Stifel.[11] (2) Both polyuria and osteomalacia occurred during the course of pregnancy and form the subject of a case report by Gentili;[12] but both polyuria and osteomalacia in this patient disappeared after delivery. (3) Daser[13] reported a case of Paget's disease associated with daily urinary output varying from 1100 to 3500 cc. A diagnosis of associated diabetes insipidus cannot be based with certainty upon the data included in the author's report. (4) Schoen[7] reported in December, 1924, the case of Paget's disease associated with diabetes insipidus to which report reference has been already made.

Case Report. D. M., a white male was born September 9, 1921. His weight at birth was $8\frac{1}{4}$ pounds, and delivery was normal. He was first seen by one of us, (Gordon), October 16, 1924, at which time the child's chief complaint was excessive thirst and polyuria. At age of twenty-one months, an injury to the head occurred; at the area of impact there developed almost immediately a lump "about the size of a quarter dollar." This lump gradually increased in size until about four months after injury when child was operated upon by Dr. L. H. Landon, who made a diagnosis of hematoma with partial necrosis. Landon now believes that the tumor was a bone cyst. Two weeks subsequent to operation, the child developed difficulty in walking. He would scream with pain when he attempted to stand and soon gave up such attempts. He was referred to Dr. David Silver. A diagnosis was made of degeneration in first lumbar vertebra and in ilium. The outer table of ilium was found to be absorbed, there being present a small cavity about 2.5 cm. by 1.3 cm. The surrounding bone seemed hard. A small amount of broken down tissue and apparent granulation were removed by curettement after which a body cast was applied. The child remained in this cast for a period of six months, at the end of which the cast was removed and a body brace substituted. While the cast was worn, vomiting, which had been of occasional occurrence since the time of the head injury, became progressively more frequent. It appeared to be of propulsive type and soon occurred regularly during the night and during the course of the following morning. There was marked anorexia and the child rapidly lost weight. Vomiting stopped after removal of the cast.

Excessive thirst and polyuria were first noted in March, 1924, or nine months after the head injury. In the beginning of this phase of his disease, the boy would drink about 1 liter of water

during the night. Water intake gradually increased until he was drinking 8 to 12 liters of water during the twenty-four hours. Urine output paralleled the water intake, as much as 4 liters being excreted during the course of a night.

Physical Examination. October 16, 1924. A child of marasmic appearance, aged thirty-seven months, whose mother desires that he be treated for excessive thirst. The child is wearing a body brace, is underweight, his skin is dry and wrinkled, the musculature is flabby and poorly developed. There is present a dry seborrhea of scalp; and a scar over left eye with ptosis of upper lid. The pupils are round and equal and react to light and accommodation; there are no extraocular palsies, the ptosis having obviously resulted from operation. The tonsils and cervical lymphatic glands are enlarged; there are no demonstrable abnormalities respiratory or cardiovascular systems. The abdomen bulges with protruding umbilicus, but is otherwise negative.

Bones and Joints. The surface of the skull is markedly uneven because of numerous elevations from split pea to quarter dollar in size. Supraorbital prominences are markedly overdeveloped, the right larger than the left. The fontanelles are closed. There are no demonstrable deformities of ribs, vertebrae, pelvis or bones of extremities; no massiveness of the inferior maxilla; the hands and feet are of ordinary size for this age.

Laboratory Findings. Urine examination: October 16, 1924, total quantity in twenty-four hours averages 8 to 12 liters. A mixed specimen shows: Specific gravity 1002; no albumin, sugar, Bence-Jones protein, or acetone. The blood picture is normal with hemoglobin of 90 per cent; the Wassermann blood test is negative and a like reaction was subsequently obtained on the blood of each of the child's parents.

Dr. David Silver kindly furnished us with the following note as to the clinical diagnosis of the bone disease, together with a laboratory report on the nature of the material removed by curettement. "The disease process present in ilium is apparently an osteitis fibrocystica. Tissue removed from ilium looks like an old pyogenic osteitis of outer table." The report on the specimen referred to the Singer Laborabory is as follows: "A tiny fragment of soft tissue, which was fixed in Zenker's fluid. On microscopic examination this was found to be very cellular. A small piece of compact bone is attached to one side. The cellular portion appears to occupy the medullary part of the bone. Two types of predominating eells are present. Of these, the more numerous are cells about the size of a large lymphocyte or lymphoblast, having a pale oval nucleus and rather abundant pale cystoplasm, sometimes clear or vacuolated. These cells are closely packed with little or no stroma; yet there is no definite architectural arrangement. Several mitotic figures are found in the cells of this type. Situated generally toward the periphery of the

groups of cells above described, are found groups of small lymphocytes, and, scattered irregularly throughout, are numerous eosinophilic leukocytes with an occasional small focus of neutrophilic polymorphonuclear cells. The general make up of the tissue, as to predominance of one type of cell with mitotic figures, is consistent with a diagnosis either of tumor or of an infectious process; but we do not feel that we can make a positive diagnosis from this specimen. The type of cell is consistent with lymphoblastoma or nongranular myeloma. No normal myeloid tissue is seen; no evidence of cyst."

Subsequent Case Record. On October 16, 1924, the patient was given a hypodermic injection of 0.5 cc. of commercial pituitrin, the water intake during the subsequent twenty-two hours being reduced to 3½ liters. On the following day the child received 0.5 cc. of pituitrin, the water intake being 2 liters for the succeeding twenty-two hours. Medication was withheld during the following two days during which time the water intake rose to 7 liters in twenty-four hours, and vomiting, which had stopped following the first injection, recurred and was severe. On October 20, 0.5 cc. of pituitrin was injected and the water intake for the subsequent fifteen hours was one liter. Subsequent to this observation 1 cc. of pituitrin has been administered on alternate days. This dosage has been found to control the polyuria for a period of thirty to thirty-six hours. While under the influence of pituitrin child showed marked subjective and objective improvement: his appetite improved and restlessness and vomiting disappeared. In a few instances pituitrin was withheld longer than forty-eight hours, always with the return of polydypsia and polyuria, loss of appetite and increase of irritability.

Radiographic Report. The material studied comprises radiograms of practically the entire body. These were made in July, 1924 November, 1924, and again in March, 1925.

In the right lateral view of the skull are four areas of bone absorption clustered in the fronto-parietal region. They are approximately 1.5 cm. by 1 cm. Five similar areas are found in the left lateral view. The largest of these, 5 cm. by 4.5 cm., is located in the lower frontal region. Two smaller ones are nearer the midline anterior to the fronto-parietal suture, and two 1 cm. by 1 cm. are in the upper occipital region. There is no evidence of abnormality in the region of the sella turcica in any of the films of the three series.

The glenoid processes of both scapulae show from three to five areas of rarefaction which are approximately 0.5 cm. in diameter. There are no abnormalities present in the ribs. The epiphysis of the greater tuberosity of the left humerus contains five small areas not more than 0.2 cm. in diameter.

The body of the first lumbar vertebra is greatly reduced in size; there is no rarefied area surrounded by normal bone. The appear-

ance would lead one to suspect that an earlier cyst had been replaced with fibrous tissue, and with subsequent decrease in the size of the vertebra.

From five to seven areas of bone absorption are found in each ilium, and in both sides of the sacrum; the left ischium shows many small areas of bone absorption: the right ischium but one.

The epiphysis for the head of the right femur reveals a circular area of lessened density about 1.3 cm. in diameter. The necks of both femora show larger areas. In the upper third of the shaft of the right femur, a central lesion, 1.2 cm. by 2 cm. that has produced expansion of the cortical bone, is present.

The general appearance of these lesions is that of a rarefied area surrounded by normal bone. They are essentially regions of bone absorption or of bone destruction without evidence of repair. The periosteum is not involved. The absorbed areas appear as cyst-like formations within the medullary cavity.

Comparing the three sets of films, we note a progressive improvement in the bone disease. The progress between November, 1924, and April, 1925, has been greater than that between July and November, 1924.

The age of the patient, the multiplicity of the lesions, the peculiar distribution and the mottled appearance of the bones would suggest a diagnosis of a polycystic osteitis.

The absence of new bone formation eliminates osteomyelitis.

The uninvolved bone shows no marked osteoporosis. Osteoporosis is usually present in osteomalacia. Osteitis deformans occurs at later age periods. The characteristic thickening of the subcortical bone in Paget's disease is absent here. Multiple giant-celled tumors do not occur in the first age period, nor do they produce so many lesions.

The multiplicity of lesions is evidence against central sarcoma. No mention is made in the literature of cysts in multiple myeloma. True enchondromata are extremely rare in the long bones.

The multiplicity of the lesions also rules out the acute infections, tuberculosis and syphilis.

Recapitulation of Roentgen-ray Report. A study has been made in a three-year old male of bone tumors or bone cysts with involvement of the cranium, the shoulder girdle, the long bones of the arms and legs as well as the flat bones of the pelvis. The tumors or cysts appear as areas of bone absorption surrounded by normal bone. The periosteum is not affected. The epiphysis as well as the diaphysis is the seat of disease. The distribution, multiplicity and mottled character of the lesions is favorable to a diagnosis of osteitis fibrosa polycystica.

Summary of Case Report. A child previously normal, at the age of twenty-one months received a head injury. At the area of contact a swelling developed which was probably at the outset a

hematoma, but which when operated upon four months later, was found to contain tissue which was apparently necrotic. The operating surgeon believes that at this time the tumor was a bone cyst. Two weeks subsequent to operation there was obtained evidence of involvement of first lumbar vertebra and ilium, involvement of other bones being noted from time to time. Examination of a fragment of tissue curetted from the diseased area in the ilium failed to lead to histological diagnosis, but Dr. David Silver believed that clinical evidence supported a diagnosis of osteitis fibrocystica. Radiographic examination of individual bones, or of the entire skeleton, was made at intervals and the radiographer believes that upon the results of these Roentgen ray findings alone a diagnosis of osteitis fibrosa polycystica can be made. Comparison of earlier with later radiograms shows that the bone disease has lessened in severity during the period of observation.

Diabetes insipidus developed nine months after the head injury and at a time when the generalized disease of bone was well advanced. It was found that the polydypsia could be controlled by hypodermic injections of pituitrin. One cc. has been injected on alternate days throughout a period of eight months during which time the child has shown marked subjective and objective improvement.

Discussion. The occurrence of diabetes insipidus during the course of a disease associated with multiple bone lesions naturally leads to inquiry as to whether the association is accidental or whether the diabetes insipidus arose as a result of the bone disease or whether the occurrence of both affections was merely due to the presence of a common cause.

Such inquiry must naturally take into consideration the etiology of osteitis fibrosa polycystica and of diabetes insipidus. Unfortunately, the cause of neither of these affections is fully known. The existence of osteitis fibrosa polycystica as an entity apart from osteitis deformans has been questioned. Diabetes insipidus is a clinical syndrome only.

Many theories have been advanced as to the causation of osteitis fibrosa polycystica. Virchow[14] believed it due to cystic degeneration and absorption in enchondromata. Boit[15] stated that most cases of osteitis fibrosa are of inflammatory origin, the others being caused by toxic agents resulting in disturbance of metabolism which in turn brought on the bone changes through the action of abnormal secretions. Rehn[16] likened the disease to hog snuffles, a phase of dystrophy in rapidly growing bones. Silver[17] and Landon[18] conclude that the cyst formation arises as the result of one of three processes—infectious, neoplastic or metabolic. McCrudden[19] writes that formation of bone cysts may be due merely to nutritive unbalance which results in calcium withdrawal, the increased catabolism of bone possibly originating through a need for calcium in other body structures. He finds that foods

low in calcium do not decrease calcium output, the resulting calcium unbalance eventually resulting in softening of the bones. Barrie[20] believes that the cystic areas are caused by a contraction of granulation tissue. He regards bone cysts, osteitis fibrosa and giant-cell sarcoma as but different phases of the same process: an attempted repair following bone destruction, the latter being probably induced by infection, trauma, malnutrition or metabolic changes due to endocrine disturbances. Von Recklinghausen[21] in his original communication states that in his belief the peculiar bone changes are a result of traumatic or mechanical factors: fibrous tissue, cyst formation and giant cell sarcoma representing different phases of the same process, namely, an attempt at repair. Lotsch[22] concludes that the underlying basis for osteitis fibrosa is a disturbance in the correlation between the glands of internal secretion. He demonstrates by animal experiments that in his series a hematoma did not lead to cyst formation. Therefore, he rejects the theory of traumatic origin of bone cysts.

That a complex association of diffuse bone disease may occur with diseases ordinarily attributed to metabolic disturbances or with diseases of ductless glands is exemplified by a case reported by Young and Cooperman[23] in which osteitis fibrosa polycystica was associated with giant cell sarcoma. In this patient a diagnosis was also made of rickets and of tumor of the hypophysis. Schoen[7] states that osteitis deformans, under which term he includes osteitis fibrosa, is often associated with dysfunction of the ductless glands. Of 11 cases of chronic bone disease associated with clinical evidence of endocrine disturbance, he finds that premature appearance of menopause occurred in 7, giantism appeared in 2, and enlargement of thyroid in 3. In 1 member of the latter group hypothyroidism was present. He believes that these combinations of disturbances of internal secretions with Paget's disease are not accidental. The special relationship of hypophysis with ovaries and bony growth is recognized. The relationship of another generalized bone disease, osteomalacia, with pregnancy and the fact that oöphorectomy or Roentgen ray treatment of the ovaries can exert a favorable influence on osteomalacia are cited as observations which support the general contention. O'Meyer and Schmorl are quoted as having described tumors of hypophysis as occurring in cases of Paget's disease reported by them. "It can only be stated that there exists a connection between changes in the glands of internal secretion and the bone disease: the problem as to the etiology of osteitis deformans is not solved thereby."

Theories as to the causation of diabetes insipidus abound. The syndrome has been noted in association with systemic bacterial infections, with encephalitis lethargica, head injury, tumor of brain or hypophysis, intoxication as occurring in pregnancy or hyperthyroidism, syphilis and tuberculosis. Heredity has been thought

FIG. 1

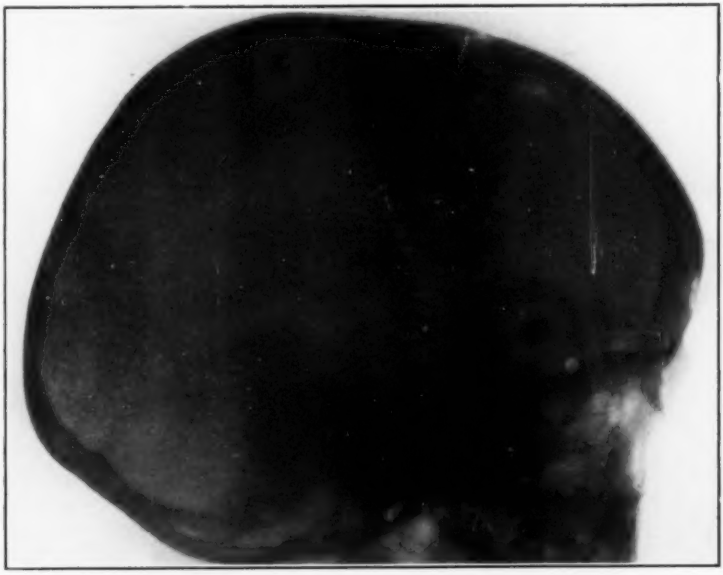

FIG. 2

FIGS. 1 and 2.—Multiple areas of bone absorption (Polycystic osteitis) in the frontal, fronto-parietal and occipital regions of the skull. Sella turcica normal.

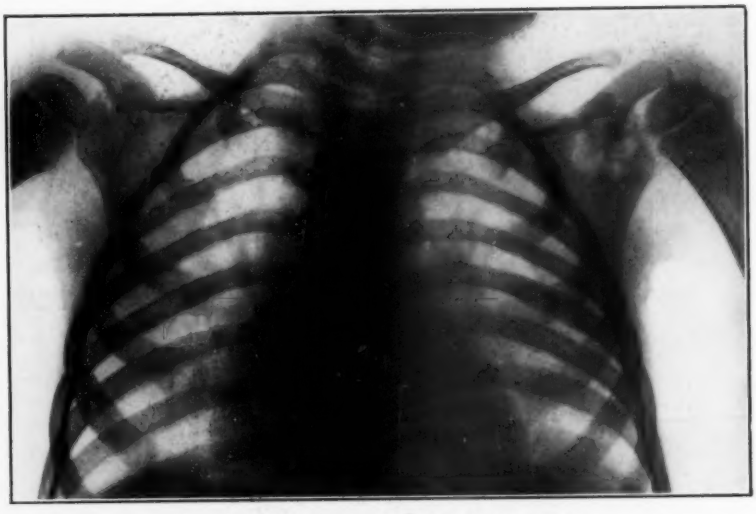

FIG. 3.—Similar areas involving both scapulæ.

FIG. 4.—Involvement of the sacrum, ilia, ischia, and heads of both femora.

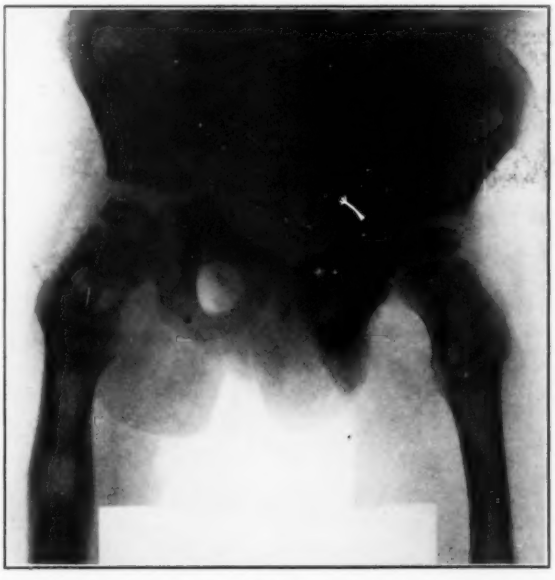

FIG. 5.—Note the lesion in the epiphysis for the head of the right femur. In the upper third of the shaft of the right femur there is a central lesion showing expansion of the cortical bone.

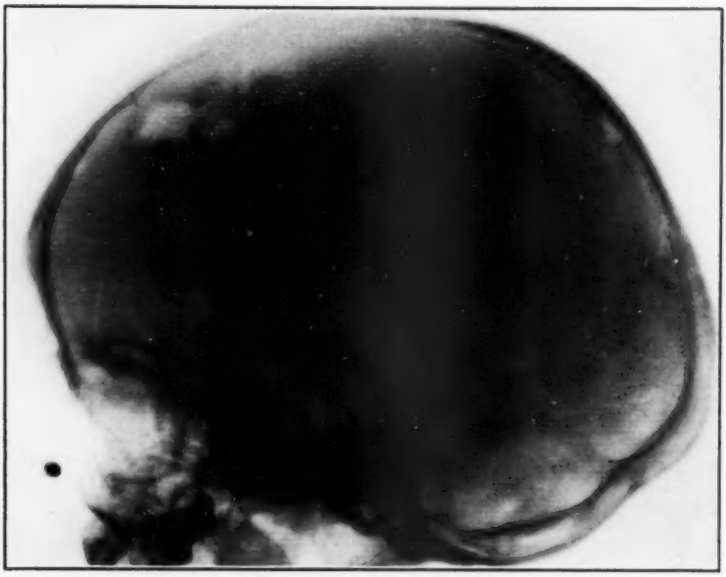

FIG. 6.—Note disappearance of lesions six months after observation and treatment.

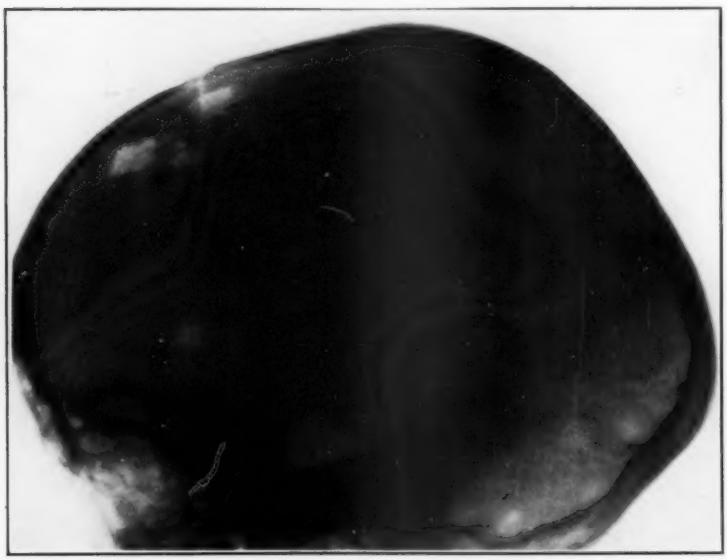

FIG. 7.—Original radiogram. Six months before present study.

to exercise an influence. Keen emotion, such as fear, has apparently precipitated an attack. Dysfunction of the posterior lobe of the hypophysis is believed by many to be the underlying cause. As adherents to this belief may be mentioned Christian,[10] Maranon,[24] Cushing,[25] Winslow,[26] Motzfeldt,[27] Stenstrom,[28] and Schoen.[7] Bab[29] attributes the polydypsia to dysfunction of the pars intermedia. Bailey and Bremer[30] Moreschi,[31] Leschke,[32] Camus and Roussy,[33] and Bauer and Aschner[34] attribute the syndrome to abnormality of the infundibular region of the hypothalamus. Abel[35] is confident that further research will demonstrate that the posterior lobe of the hypophysis together with the pars intermedia and similarly functioning tissues of the hypothalamus elaborate a specific hormone which controls a removal of water from the kidneys and perhaps from other organs. He asks whether it is an entirely untenable supposition that a deficiency of this hormone should lead to a polyuria or diabetes insipidus. Abel[35] states that the experiments of Camus and Roussy[33] do not prove that polyuria is not produced by injury to the nerve centers of the hypothalamus, even though these experiments show that piqure produced polyuria whether in presence of the hypophysis or after removal of that structure. Injury to any part of brain results in a profound influence on the entire brain structure. Hence, injury to hypothalamus may have resulted in failure of the hypophysis to produce a hormone, or it may have interfered with the entrance of such hormone into the capillaries or cerebral spinal fluid. On the other hand, temporary diabetes insipidus has been frequently described as following extirpation of the hypophysis.

Bab,[29] Leschke,[32] Gorke,[36] and Rosenbloom and Price[37] believe that polyuria is due to an inability of the kidney to concentrate salts. On the other hand, Hecht,[38] and Allen and Sherrill[39] state that polyuria cannot be due to such functional disturbance of kidney. Tierney[40] quotes Rabinowitch as believing that diabetes insipidus is produced by the lack of some internal secretion which normally regulates diuresis by acting on renal cells. Cushing[25] attributes polyuria to lack of normal stimulation of the vaso-motor nerves of the kidneys and other parts of the central nervous system.

In speculating as to the existence of a possible relationship between the osteitis fibrosa polycystica and the diabetes insipidus which were associated in our case, we have first taken into account the fact that while but one case has been reported which bears a close resemblance to our own, nevertheless, several cases have been observed in which an association of degenerative bone lesions with persistent polyuria has been recorded. We also have borne in mind the fact that osteitis fibrosa may be recognizable only as a result of extensive roentgenological examination. It is thus made evident that osteitis fibrosa may be readily overlooked by an internist, while an

orthopedist, whose attention is especially directed toward disease of bone, may fail to notice or record polydypsia and polyuria. In other words, an association of these disorders may be more common than is indicated by case reports.

It is our belief that in our patient, as in Schoen's,[7] the association was not accidental. Whether the initial head injury were responsible for the generalized osteitis fibrosa or for the diabetes insipidus or for both, must remain an open question. Authors have been quoted who believe that each of these conditions can be produced by cerebral trauma. Lotsch's animal experiments merely prove that bone cyst did not follow hematoma under experimental conditions in the animals studied by him. His conclusions must be accepted with reservation as applied to man.

Dysfunction of the ductless glands has been evoked as one of the etiological factors in producing generalized bone disease, and it is also given a prominent place among the etiological factors of persistent polyuria. There is some clinical and experimental evidence to support this view. This evidence is stronger in the case of diabetes insipidus than in that of generalized degenerative disease of bone, but even in the former instance the supposition as to the etiological influence of disturbances of internal secretion is perhaps as acceptable as any. The prompt control of our patient's polyuria by hypodermic injections of pituitrin, together with the roentgenological evidence as to the improvement of the osteitis fibrosa during the period of pituitrin administration may be mentioned as clinical observations which offer some support to the supposition that deficiency of the pituitary hormone may have played a part in bringing about both of the conditions named.

Is roentgenological evidence that a sella turcica may cast a normal shadow proof that no disturbance of pituitary hormone exists? To this question one may unhesitatingly answer in the negative. It is probable that not only the hypophysis but also the pars tuberalis and a portion of the hypothalamus immediately contiguous with the upper part of the hypophyseal stalk possess like functions to those of the posterior lobe and pars intermedia of hypophysis. It is possible that they possess like functions to those of the anterior lobe as well. In other words, these structures exercise some control over urinary excretion; they may also regulate to some extent the function of bony growth. If this be true, then modification of hypophyseal function may occur in the presence of a structurally normal hypophysis.

Clinicians have frequently observed that diabetes insipidus first appeared after head trauma. We have in our case a history of trauma; but the late appearance of diabetes insipidus would indicate that the latter was not directly due to the initial skull injury. In the patient described by Schoen[7] it was noticed that the base of the skull was extremely massive and compact. Sinuses were not defi-

nitely recognizable and the roof of the skull was strikingly thickened. The sella turcica showed no decrease in size, but the occurrence of polyuria is attributed to abnormal bony growth in the region of the hypophysis, thickening of the skull occurring at the expense of the size of the cavity. Such thickening of bone was not shown in our case, but the possibility of its existence cannot be denied. Therefore, may it not be accepted as a reasonably satisfactory hypothesis, as perhaps a guess not susceptible to proof, that in our patient hematoma following injury to the skull was succeeded by local bone cyst, that there followed, because of influences not at present understood, a generalized osteitis fibrosa, and that as a result of this bone disease, there resulted alteration in hormones supplied by the hypophysis and other structures with which it is physiologically allied? If this hypothesis be correct, then the occurrence of the diabetes insipidus is explained.

Summary. A case is reported in which occurred the exceedingly rare association of osteitis fibrosa polycystica with diabetes insipidus. The generalized bone disease followed local trauma to skull. The polydypsia and polyuria did not appear until the osteitis fibrosa was well advanced. We have speculated as to whether the association was accidental, whether bone disease and diabetes insipidus were due to the presence of a common cause, or whether the bone disease was indirectly responsible for the persistent polyuria. This report is made in the hope that it may eventually throw some light upon the obscure etiology of both osteitis fibrosa and of diabetes insipidus.

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THE HUMAN CEREBROSPINAL FLUID IN SYSTEM AND DIFFUSE DEGENERATIVE DISEASE INVOLVING THE NERVOUS SYSTEM.*

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There are very few of the degenerative, infectious or system diseases in which careful and consistent studies of the spinal fluid have been undertaken. For the most part, reports in the literature cover isolated cases and one always questions their reliability, since other physical factors may not have been considered. The only evidence admissible upon which conclusions may be based comes from those who have made a group study of some special condition and reported all the findings from both clinical and laboratory standpoints. From such materials, one is reasonably safe in tabulating statistics.

Multiple Sclerosis. Few other conditions conscientiously investigated thus far have revealed the marked cerebrospinal fluid findings that are reported in multiple sclerosis. Ayer and Foster[1] reported the findings in 38 verified cases in 1921. They found no pressure alterations beyond the normal. The cell counts in 48 specimens of fluid showed 0 to 5 cells in 61.2 per cent, 6 to 10 cells in 16 per cent 11 to 20 cells in 4.2 per cent and 42 cells in 2 per cent.

The total protein showed an increase in 50 per cent of cases; the globulin reaction was negative in 22 cases and positive in 9. The Wassermann reaction was negative throughout. The gold-chlorid test gave more definite findings than any other estimation. Forty-two readings were made, showing a "paretic" type of curve in 21 fluids (16 patients), a "luetic" type in 7 fluids (7 patients), positive reactions in 3 fluids (3 patients) and negative reactions in 11 fluids (10 patients). This shows that the "paretic" curve

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was obtained in one-half the number of fluids examined and nearly one-half the number of cases.

Sugar averaged 0.048 per cent in 14 fluids. Nonprotein nitrogen averaged 21.5 mg. in 11 determinations. The average in 11 determinations of chlorid content was 688 mg. per 100 cc. No acetone bodies were found. Creatinin averaged 1.78 per 100 cc, and urea 15.5 mg. per 100 cc.

Eskuchen[2] found 3 out of 4 cases to have entirely negative fluids; the fourth case showed a pleocytosis, increase of globulin and a paretic gold curve. Jaeger and Goldstein[3] reported, in a few cases, a "slight colloidal-gold reaction, there being a faint color change in the first 4 to 5 tubes." Flesch[4] reports 8 cases, showing a completely negative fluid in 1 case, a slightly positive colloidal-gold curve with other tests negative in 1 case, and a paretic-gold curve in the remaining 6 cases. Kaplan[5] reported 2 cases in which one had a negative and the other a paretic-gold curve. Later, he reported 18 cases[6] in which but 1 had the paretic type of curve. Oetiner[7] found the globulin increased in 1 case with other findings negative, and 1 case with no pleocytosis or globulin but with a partial reduction in the colloidal-gold reaction.

Rolstadt[8] stated that in 75 per cent of cases there is no cellular increase in multiple sclerosis. Moore[9] states: "Together with the clinical evidence, it is believed that the spinal fluid picture is fairly constant and that, other things being equal, such a picture is a strong argument in favor of a diagnosis of multiple sclerosis. In its absence, the diagnosis becomes at least doubtful." Eskuchen[10] at a later date (1919) reported that multiple sclerosis in a large percentage of cases showed typical tabetic or paretic curves. Sicard[11] found 2 cases with a pleocytosis and 5 cases without it. Eskuchen[12] again states that the spinal fluid findings vary, 50 per cent showing a normal fluid. In 30 per cent of cases, the pressure was slightly increased, the globulin weakly positive, the cell count 20 to 30 and the gold reaction of the "luetic" type The fluid Wassermann reaction was negative. In about 20 per cent of cases the pressure was definitely increased, the globulin moderately positive, the cell count 30 to 50, the fluid Wassermann negative and the gold curve of the "paretic" type. Boyd[13] examined the fluids in 18 cases, finding the fluids clear, pressure normal, the cells varying from a slight to a moderate lymphocytosis, but never exceeding 30, and the globulin slightly increased. On the other hand, Mestrezat[14] found 3 fluids negative in every respect. Tucker[15] in 4 cases of multiple sclerosis, noted that the pressure varied in each case, that cells numbered not more than 5 and the gold curve was of the paretic type in only 1 case.

A review of selected hospital case records with serological studies and typical clinical syndromes, shows that the current literature is in agreement for the most part. Time did not permit the exhaustive

survey that the subject demands, and it is regrettable that necropsy confirmation is not obtainable in the majority of instances. However, basing conclusions on the material at hand, there were found: normal appearance and pressures of fluids, not infrequent cellular increases, occasional increases in globulin content, and gold-sol curves ranging from negative, atypical and luetic to paretic types. The paretic types occurred in less than one-third of all cases. Ayer and Foster[1] mention the variation in types of curves in the stationary and progressive cases, finding the paretic type most commonly in the latter. To this observation, there might be added the age factor, for in 6 cases personally observed where definite clinical symptoms were present, the indefinite or negative curves were found in patients between fifteen and thirty years of age, while the paretic curves were the rule in the thirty to forty-five age periods. This naturally raises the question of the time of onset of the disease and whether it might not originate at a much younger age period than we are led to believe by the usual histories.

The figures for sugar content have varied remarkably and show no uniformity. The same is true of the protein constituents of the fluid. These two substances have no apparent relationship to the colloidal-gold reaction. In a few cases in which the chlorids were estimated, they were found high, usually over 600 mg. per 100 cc.

The Encephalitides. Few studies are reported in spinal fluids of cases of encephalitis. Frequently the type of encephalitis is not known, the term used being merely "acute encephalitis." This does not lend itself to conclusive survey reports. However, in those cases reported, some findings are worthy of mention. Sicard[11] reported no other findings than a marked polynucleosis. Eskuchen[12] stated that in pure encephalitis, no changes in the fluid could be found, except where meningitis coëxisted and then the typical findings of meningitis were present. Polioencephalitis had no effect upon the fluid findings.

In epidemic encephalitis many reports have been made, in fact the figures from some thousands of cases are available. The findings may be said to be consistent only in their inconsistency.

Bassoe[16] reported clear fluids under increased pressure, globulin slightly increased, but the colloidal-gold reduction in the luetic zones in practically all cases.[18] The cell count varied, being less than 10 in 6 cases, 10 in 1 case, 25 in 1 case and 26 in 1 case. Neal[17] studied 40 cases. She found the cells to be slightly or moderately increased, occasionally reaching 150 to 200; lymphocytes predominated. It was further noted that the cell counts fell off very quickly. Globulin was greatly increased. The gold curve was of the luetic type in some cases, but was not common. Sugar was increased in amount.

Brill and Benson[18] in a study of 13 cases with special reference to the Lange reaction found a reduction in the luetic zone in all

cases. Flexner[19] in a general investigation of this disease, noted an increased pressure of the fluid, which was clear. The number of cells were slightly increased—rarely reaching 100 to the c.mm., but usually around 10 to 20, and mostly of the lymphocytic variety. He found also that globulin was slightly increased.

Davis and Kraus[20] reported the findings in 34 cases. Here 42 per cent showed changes in the gold curve, usually in the luetic or meningitic zone. There was no relationship between the stage of the disease and the gold solution readings. Two cases showed a paretic type of curve. They finally concluded that "abnormal colloidal-gold reactions are evidence of pathological changes and not of specific etiology." Later, Kraus and Pardee[21] summed up the reports to that time, for presentation before the Association for Research in Nervous and Mental Diseases. In their review of the literature, Von Economo and Neal are quoted. The former found an excess of globulin, the cells ranging from normal to 43, the pressure increased in some cases and the colloidal gold negative. The latter pointed out abnormal changes in the gold curve and mentioned the similarity of the curve to poliomyelitis. Following this, observations on the occurrence of syphilitic and paretic types of curves were made by Bassoe, Brill and Benson, Davis and Kraus, and Archambault.

The fluids were reported as clear and colorless in the majority of cases but "bloody fluids have occasionally been found, in fact more commonly than could be accounted for by the puncture of a vein." The pressure varied from normal readings to a considerable increase. The cell counts found by the French differed from those of Von Economo. The French stated that a normal cell count was a rule and was of diagnostic significance. The English and American observers, however, have found a pleocytosis. The cells are predominantly of the mononuclear type. "The impression gathered from the literature is that the number of cells may vary from normal to an increase of several hundred."

The globulin was increased in a majority of cases. Sugar, whenever reported, has exceeded the normal limit, figures varying from 0.067 to 0.106 per cent. The Wassermann reactions have been uniformly negative. The gold curve in Von Economo's report showed "no typical elevations."

The contribution of Kraus and Pardee then summarizes 245 cases. The fluid findings were as follows: (1) Clear, colorless fluids; (2) increase in spinal fluid pressure; (3) increase in number of mononuclear cells; (4) increase in amount of globulin; (5) increase in amount of spinal fluid sugar; (6) a negative Wassermann reaction; (7) the presence of bodies producing a change of a solution of colloidal gold (Lange).

The number of cells is greatest in the first three weeks of the disease. Fluctuation in the number of cells occurs during the

disease, an increase occurring in remission. The globulin was increased to a moderate degree in 72 per cent of cases. The sugar in 12 cases varied from 0.062 to 0.095 per cent. The Wassermann reaction was negative. The colloidal-gold curve was changed in 83 per cent of cases (100 out of 120 cases). The type of curve varies considerably, there being a tendency to elevation of the left hand part of the curve in later stages, but this was not constant. Changes did, however, occur in the middle zones.

TABLE I.—SPINAL FLUID FINDINGS IN ENCEPHALITIS.

Case No.	Pressure.	Cells	Globulin.	Wassermann reaction.	Colloidal gold.	Sugar, per cent.
1	Normal	2	+	Neg.	Neg.	
2	4 mm.	1	+	"	"	
3	8 mm.	7	+	"	"	
4	+	10	+	"	"	
5	Normal	5	+	"	"	
6	Normal	3	+	"	"	
7	+	1	+	"	"	
8	Subnormal	15	++	"	"	
9	Slow increase	3	+	"	"	
10	Slow increase	2	+	"	"	
11	Slow increase	12	+	"	"	
12	Normal	0	+++	"	2211100000	
13	++++	22	++++	"	Neg.	
14	+	0	++	"	"	
15	16 mm.	2	+	"	"	
16	+++	1	++	"	2110000000	0.07
17	12 mm.	11	+	"	Neg.	
18	Normal	10	+	"	"	
19	Normal	2	+	"	"	
20	+++	1	++++	"	"	
21	Slow increase	10	+	"	"	
22	+	20	+	"	"	
23	Normal	3	+++	"	"	
24	Normal	2	+	"	"	
25	Slow increase	12	++	"	"	
26	Normal	2	+	"	"	
27	Normal	2	Normal	"	"	
28	Normal	6	+	"	"	
29	Slow increase	7	+	"	"	
30	Increase	18	Normal	"	"	
31	++++	5	++	"	"	
32	Normal	3	++	"	"	
33	Slow increase	9	++	"	"	
34	22 mm.	0	Normal	"	"	
35	Normal	4	+	"	"	
36	4 mm.	5	+	"	"	
37	Normal	4	+	"	"	
38	40 mm.	50	++	"	"	
39	+	0	++	"	2221100000	
40	Normal	4	+	"	"	
41	+	5	+++	"	"	0.075
42	++	0	++	"	"	0.068
43	+++	0	++++	"	"	0.06
44	+	8	+++	"	"	
45	12 mm.	15	+	"	"	

Levinson[22] reported the fluids in encephalitis epidemica as colorless, with increased globulin, and cells usually increased to from 10 to 50. An increase in globulin without a corresponding pleocytosis was a not inconstant finding. Tucker[15] in a contribution to this compilation, reported on 45 fluids (see Table I). He found the pressure variable, being subnormal in 2 cases while it reached 50 mm. in 1 case. The cell counts ranged from 0 to 50; from 0 to 10 in 33 fluids; from 10 to 20 in 9 fluids; 20, 22, and 50 in 3 respective fluids. The globulin was normal in but 3 fluids; slightly to moderately increased in 35 fluids, and definitely increased in 7 fluids. The Wassermann was consistently negative. The gold curve was negative in all but 3 fluids, each of these showing a reduction in the left-hand tubes. Sugar is reported as negative in all but 4 cases, and here it ranged from 0.06 to 0.075 per cent.

Extracts from hospital records from various sources bear out the foregoing, and in particular the inconsistency of spinal fluid findings. In all cases the fluids were clear. The pressure, when recorded, was normal or moderately increased, the globulin either negative or + 1, occasionally + 2 and rarely + 3. The Wassermann reaction was consistently negative. The sugar content was not estimated in the majority of cases, but the few observations made showed a range from 0 to 0.110 per cent as the two extremes, while the most of them fell between 0.040 and 0.075 per cent, the average being 0.062 per cent.

In this connection the research of Alpers, Campbell and Prentiss[23] is of distinct significance. They found a great variation of spinal fluid sugar in a small series of normal cases and conclude that the normal content is as yet not correctly estimated. In epidemic encephalitis, they concluded from reports in the literature that there was considerable doubt as to the significance of increased sugar percentage. They studied the fluids from 35 patients with encephalitis and found an average of 82.1 mg. per 100 cc. This contrasted with an average of 45.3 mg., in untreated paresis; 55.4 mg. in treated paresis; 80.1 mg. in dementia precox; 66.9 mg. in manic depression psychoses, and 123 and 189 mg. in 2 cases respectively of diabetes. By considering the normal fluid to contain from 50 to 65 mg. of sugar per 100 cc, it is evident that their cases of epidemic encephalitis showed a distinct increase. The hospital records mentioned above would then indicate a normal sugar content.

The gold solution curves could in no sense be considered typical, except that in the majority of cases they were negative. Unfortunately, however, the stage of the disease is not mentioned in some instances, which precludes reliable conclusions.

Poliomyelitis. The first note appearing in the literature of spinal fluid findings in poliomyelitis is found in 1902 in an article written by Sicard.[11] In it he states that the cells are greatly increased in the acute stages and are mainly lymphocytes.

Gay and Lucas[24] in 1910 published the results of an experimental study of poliomyelitis in monkeys. They found in 6 cases of monkey poliomyelitis, that the cytology of the incubation period showed 100 to 300 cells. In the prodromal period, the cells rose to 100, and 60 per cent of them were polymorphonuclears. In the early acute stage cells were definitely increased but had a predominant lymphocyte percentage. At the end of a week or ten days, there were few cells left.

Abrahamson[25] reviewed the literature in 1912 and reported as follows: Forbes[26] studied 33 fluids of which 6 were bloody. Twenty-four had albumen in varying amounts, 6 a heavy precipitate. Twenty-one fluids had an increase in cells, the cellular elements being in direct proportion to the albumen content. Morse[27] examined 13 fluids, finding them all clear and cells increased in all of them. Abrahamson studied 43 fluids. Fifteen fluids showed a great increase of cells, 24 a moderate increase and 4 no increase. Small mononuclear leukocytes predominated in 88 per cent of cases. The albumen content was increased in 52 per cent of cases. He found no relation between the albumen-globulin ratio and the stage of the disease. The sugar was tested in 15 fluids, 12 giving a good reduction and 3 a weak reduction. Curiously enough, the fluids having a weak reduction were the most severe cases clinically.

The best article published on the subject was by Peabody, Draper and Dochez in 1912,[28] a monograph from the Rockefeller Institute. Sixty-nine patients formed the material for the study made and from these cases 233 fluids were obtained and examined. Their conclusions may be summarized as follows: 1. The fluids from the early cases of the disease and especially before onset of paralysis tend to show an increased cell count with a low or normal globulin content. At this stage, the polymorphonuclear cells may be 90 per cent of the total. Most fluids, however, show almost exclusively lymphocytes and large mononuclears. 2. After the first two weeks, the cell count usually drops to normal or nearly normal, and there is frequently an increase in globulin content. A slight increase in globulin may persist for seven weeks or even longer. 3. The fluids in abortive cases are analogous. 4. The examination of the cerebrospinal fluid in acute poliomyelitis, while giving as far as is yet known, no specific diagnostic criteria, is of the utmost value as an aid to diagnosis, both in the preparalytic and abortive cases.

Batten[29] agreed that results in fluid examinations in poliomyelitis were variable, but that some cases showed an excess of albumin, with a moderate increase of lymphocytes. In some cases a very large increase of cells was found. For the most part, the stage of the disease and its location influenced the findings, those cases with the most marked meningeal involvement giving most findings in the spinal fluid.

Hayne and Cepelka[30] studied 30 cases of poliomyelitis clinically,

including the examination of the cerebrospinal fluid. They found: (1) The pressure normal in 25 cases and slightly increased in 5 cases. (2) The cells varied from 8 to 98 averaging 30 to 50.3. The globulin was increased in 16 cases.

Kolmer, Freese, Matsunami and Meine[31] reported a study of 868 fluid specimens from poliomyelitis in the Philadelphia epidemic of 1916. The conclusions were: (1) The majority of fluids were of a watery color, 1 to 2 per cent only showing a faint turbidity. (2) Seventy-two per cent of fluids from all stages showed an increase of total cells; in 80 per cent of these cases the counts were not above 100 cells per c.mm. An increase in the total cells was found in the preparalytic stage and this increase was present in 95 per cent of cases for at least three weeks after the onset of the paralysis, after which the number of cells gradually decreased. (3) In over 96 per cent of the fluids from the onset of paralysis, small lymphocytes predominated. (4) An increase in protein was found in 32 to 42 per cent of fluids. (5) During the acute stages the fluids of 40 to 50 per cent of cases yielded a colloidal-gold reaction of luetic and meningitic zones types. (6) All fluids gave a negative Wassermann reaction.

Jeans and Johnson[32] found in 100 spinal fluids examined that the colloidal gold showed a definite reduction in the luetic zone in every case, regardless of the stage of the disease. No mention is made of the cellular contents of these fluids.

Felton and Maxey[33] examined 57 fluids. They reported: (1) In the acute stages of poliomyelitis, the spinal fluid reacts with colloidal gold in zone 2 of the curve (dilutions 1 to 40 to 1 to 160), that is, in the luetic zone. (2) In the second and third weeks, the reaction is practically the same as in the acute stage with a tendency to clear up in some cases and a precipitation in the higher dilutions in others. There is no constant rule. (3) In the fourth to the eighth week, the colloidal-gold reaction runs practically with the globulin albumen content, persisting in some cases to the eighth week and beyond, but still occurring in dilutions of 1 to 40 to 1 to 160.

Eskuchen[12] mentions only a mild pleocytosis and a positive globulin reaction. Boyd mentions that the fluid pressure is generally definitely increased but may be normal. It is usually clear, but may be cloudy. The cells vary with the stage of the disease, the count being high in the earliest stages and consisting of polymorphonuclears and lymphocytes in varying proportions. He states that the polymorphonuclear high percentages occur in the earlier stages. In the prodromal stage, Peabody found the lowest cell count to be 34 and the highest 1980. The cell count rapidly falls as the disease progresses and the polymorphonuclears are replaced by lymphocytes. Globulin was increased in a ratio inversely proportionate to the cells; slight in early stages and increasing as the disease progressed. The maximum globulin content was found in the third

and fourth weeks but was never excessive. Neal[17] reported a true hemorrhage and Froin's syndrome in 2 cases. Boyd[13] stresses the sugar estimation as being of great importance in differential diagnosis. The fluids of poliomyelitic patients gave a well marked Fehling reduction, while other diseases with which poliomyelitis might be confused showed a decrease in sugar content. The colloidal-gold reaction was very constantly a luetic curve. The reaction was most marked in the first week and after the fourth week was diminished or had disappeared.

Levinson[22] stated that the fluid might be normal in every respect after the preparalytic stage. He found the amount increased by 20 to 50 cc., the pressure increased by 300 to 700 mm. of water and the colloidal-gold reaction either showing no curve or else a change in the luetic zone. He found also, that the cells were in greatest numbers during the first week after the onset of paralysis. The majority of cells were lymphocytes (60 to 90 per cent) except in the early stages where polymorphonuclears predominated.

A review of hospital records in both acute and chronic poliomyelitis differs in no respect from the above.

Epilepsy. Mestrezat[14] states that the majority of fluids are normal in idiopathic epilepsy. There may be a slight increase in albumen and sugar. Lochelongue[34] reported the fluids normal in epilepsy and the cell count within normal limits.

Eskuchen[12] noted that in the majority of cases of idiopathic epilepsy the fluid was unchanged except that the pressure was elevated during an attack. He states that the globulin may be increased and that there is seldom a pleocytosis.

Levinson[22] made the same observations concerning increase of pressure during an attack. He also believes there is an increase in the amount of fluid during an attack but that there may or may not be an increase in the intervals.

Donath[35] found chlorin in crystals and by chemical tests in 18 out of 21 cases of idiopathic epilepsy. This observation has not been corroborated by others, the investigation apparently not having been undertaken.

One hundred hospital case records and statistics compiled by Tucker showed as follows: (1) Fluid always clear. (2) Pressures (reported in 36 cases) normal to slightly increased. (3) Cells consistently within normal limits. (4) Globulin negative to slightly increased. (5) Wassermann reaction negative (those showing a positive reaction were excluded). (6) The gold solution curve negative or showing a slight reduction (in 9 fluids).

Arteriosclerosis. In generalized cerebral arteriosclerosis without focal disease, the fluid is practically unchanged according to Eskuchen.[12] There may be a slightly positive globulin reaction and a mild pleocytosis. With encephalomalacia, pleocytosis and globular increase are frequent findings.

A study of many hospital case records reveals a distinct difference in the fluid findings of uncomplicated cerebral arteriosclerosis and in hemorrhage, thrombosis and embolism. In arteriosclerosis there were found no changes in pressure, color, number of cells, sugar or colloidal-gold reactions. In hemorrhage, the cellular elements were naturally increased in many cases because of the presence of blood, but in those cases in which the fluid was clear, about 33 per cent showed a moderate pleocytosis, with the majority of cells of the lymphocytic type. Occasionally large mononuclears were found and rarely a small number of polymorphonuclears. In one-half the cases, sugar was definitely though not markedly increased. Other findings were normal. In embolism and thrombosis, the sugar content was mainly affected. Here high percentages were found. Alpers, Campbell and Prentiss[23] have reported similar observations.

Amyotrophic Lateral Sclerosis. Mestrezat[14] studied the fluids in 2 cases of amyotrophic lateral sclerosis and in 1 case found the albumen and chlorid content normal, but the sugar very much increased. In the other case there was a slight hyperalbuminosis and a mild leukocytosis. Eskuchen[12] found a mildly positive globulin reaction, and the other contents normal.

Hospital case records show no changes of any character, so far as the ordinary routine examinations of the spinal fluid are recorded. No apparent independent and thorough investigations have been carried out in this disease.

Syringomyelia. In 1 case of syringomyelia studied by Mestrezat[14] an increase in albumen and sugar was found, all other findings being normal. Eskuchen[12] and Sicard[11] record all findings normal. Boyd[13] quoting Kaplan stated that there may be a marked protein increase without pleocytosis. He mentioned 1 case with a xanthochromia. In 4 other cases the fluids were normal.

In several hospital case records, the fluids were found clear, cells normal, globulin absent except in 1 case, sugar content slightly increased in 33 per cent, and the gold solution negative.

Cerebral Tumors. Lochelongue[24] stated that in cerebral tumors, the fluid pressure was usually increased, the albumin content normal, sugar increased, at times a moderate lymphocytosis and the chlorids normal or nearly so. Boyd[13] reported that the pressure was sometimes enormously increased and usually definitely increased. The cell count as a rule was normal but might be increased. The protein content as a rule was not increased, but more likely to be so if the tumor was a gumma. Rehm is reported by Boyd as recording the presence of cholesterin crystals and fat in cholesteatoma of the base of the skull. Boyd found cholesterin ester crystals in a tumor of the optic chasm.

Alpers[36] reports a study of 102 ventricular fluids in cases of tumor of the brain, with particular reference to the Lange gold test. In

his cases, the cells were increased in 9 instances; between 7 and 20 in 7 fluids, 73 in 1 fluid and 375 in 1 fluid. The quantitative albumen was increased in 37 fluids, total proteins increased in 45 fluids and the colloidal gold reduced in 35 fluids. The gold solution curve, however, was not uniform and reductions did not take place at all frequently in the socalled "tumor zone." He states: "most of the cases showed a reduction in the luetic or tabetic zones."

Huntington's Chorea. Eskuchen[12] reports no characteristic changes.

Hospital records confirm Eskuchen's report.

Paralysis Agitans. Eskuchen[12] reports no characteristic changes in this disease. Hospital case records, however, have shown that there is a gold-solution reaction in a majority of cases. In 10 case reports, there was a reduction in 7 fluids. In all but 1 of these the reduction occurred in the middle tubes (0001121000) slight in most instances, but moderate in 2 fluids (0233454210). In every other respect the fluids resembles those found in arteriosclerosis.

Subacute Combined Degeneration. Boyd[13] examined 2 fluids in this condition and reports the globulin slightly increased. The cells and other constituents were normal. In his report, Kaplan is quoted giving a description of 3 cases with a marked globulin increase and no pleocytosis.

A study of hospital case reports shows a clear fluid, normal pressure and cellular content, globulin absent or slightly increased in a few cases (2.3 per cent), sugar quite variable, Wassermann negative, and the colloidal gold negative in 98.5 per cent. Those fluids showing a gold solution curve gave no uniform reduction.

Spastic Spinal Paralysis. This disease is not, strictly speaking, a clinical entity but usually a part of some process in which spasticity is a predominating feature. It therefore should show, insofar as cerebrospinal fluid determinations are concerned, a reaction consistent with the underlying condition. Eskuchen stated that the fluid is for the most part normal, though there is often a mild pleocytosis and a mildly positive globulin reaction. No pleocytosis was found in any of the hospital case records reviewed.

Spinal Muscular Atrophy. Eskuchen[12] found an increase in pressure of the spinal fluid, but otherwise no uniform changes. Mestrezat mentions a similar result.

Brain Abscess. Levinson[22] found that in early brain abscess the fluid was clear and under slightly increased pressure. The cells approximate 9 to 10 per c.mm. The globulin may be slightly increased. In later or terminal stages a localized meningitis may occur and in some cases the abscess may break into the subdural space and the fluid then becomes that of a pyogenic meningitis.

Boyd[13] states that the cerebrospinal fluid may be perfectly normal in brain abscess, especially if the lesion is deep seated. If the abscess communicates with the subarachnoid space, a purulent meningitis,

with characteristic findings, results. Even in deep-seated abscess, there may be an increase in cells and globulin.

The writer's personal observations and review of case records agrees with the above.

Tetanus. Nineteen spinal fluid reports only are available for consideration in tetanus. Complete examinations were not carried out in all cases, therefore, any conclusions must be considered as tentative. The pressure is recorded as increased in 1 case. The fluid was clear in 9 cases, cloudy in 5 cases and not recorded in 5 cases. The cells varied and are reported as normal in 2 cases, as consisting of 90 to 95 per cent polymorphonuclears in 4 cases, as mainly lymphocytes in 7 cases (and presumably in the 2 normal cases), and not recorded in 6 cases. In all but the 2 normal cases and 3 in which the numbers are not given, the cells are definitely increased.

The globulin reaction is reported in 18 cases, negative in 4, doubtful in 4, definitely increased in 5, moderately increased in 2 cases. The sugar showed a marked increase in all but 4 cases and 1 case was not reported. The colloidal-gold reaction was tested in 7 cases, 5 being practically negative and 2 showing moderate reductions in the third to seventh tubes.

Rabies. One spinal fluid report is available. This shows an opalescent fluid, 60 per cent polymorphonuclears and 40 per cent lymphocytes, albumin 2 +, globulin 2 + and sugar 3 +.

Degenerative Conditions. A number of congenital and degenerative diseases, and birth injuries are grouped. These include the mental deficiencies. tuberous sclerosis, Friedreich's ataxia, amaurotic idiocy, spina bifida, Thomsen's disease, Alzheimer's disease, progressive spinal muscular atrophy, bulbar paralysis and hydrocephalus.

Eskuchen found no fluid changes in bulbar paralysis, Alzheimer's disease, mental deficiency or Little's disease. In the latter condition Eskuchen quotes Holzman as finding increased pressure in 1 case and Plaut, Rehm and Schottmüller a lymphocytosis. In 1 hospital case I found both increased pressure and a pleocytosis but other findings were negative.

In 23 case records on hydrocephalus, the fluid changes are not typical in any way. Fluids were clear in all but 1 instance; cells were increased in 6 cases; but the globulin reaction was negative in 9, doubtful in 5 and increased in 8. Sugar was increased in 13 cases and not reported in 2. The Wassermann reaction was negative in all cases in which it was reported (50 per cent). The colloidal-gold curve is given in 8 cases, being negative in 4, showing a mild reduction in the first 5 to 6 tubes in 3 cases and a stronger reduction in the last 5 tubes in 1 case.

Friedreich's ataxia, dystonia musculorum deformans, tuberous sclerosis and Thomsen's disease showed normal findings throughout.

One case of spina bifida had 26 cells, but other findings negative.

The birth injury cases showed pleocytosis and increased sugar percentages, but otherwise normal findings.

The fluid in progressive spinal muscular atrophy is reported as negative in all respects.

Amaurotic idiocy (1 case) showed a very slight increase in cells and a luetic curve.

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Foot Note.—Cerebrospinal Fluid Reports received from various New York City Hospitals and Clinics, from hospital studies made by Beverley R. Tucker, Richmond, Va., and from the Philadelphia General Hospital, The Orthopedic Hospital and Infirmary for Nervous Diseases and the Polyclinic Hospital of Philadelphia.

THE ELECTROCARDIOGRAM IN MYXEDEMA.

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and

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In 1918 White and Aub[1] published a series of 21 cases of hyperthyroidism and 2 of hypothyroidism comparing the parallelism between the metabolic rate and the amplitude of the *T* wave in the electrocardiogram. In the cases of hyperthyroidism they found a very limited parallelism between the height of the *T* wave and the percentage increase of the basal metabolism over the normal; but in the 2 hypothyroid cases, one, a patient with myxedema, and the other a Cretin, the amplitude of the *T* wave was below normal and increased after the administration of thyroid gland.

Since then electrocardiograms of 14 other cases of myxedema have been obtained at the Massachusetts General Hospital. Basal metabolic rates have also been determined before receiving any treatment, and subsequent electrocardiograms and metabolic rates were obtained on 10 of these cases after treatment. In the first electrocardiogram in every case there was a decrease in the height of the *T* wave in Lead II below normal, the highest reading being +1 mm., whereas the *T* wave in Lead II should normally have an upright deflection of 2 mm. or more. Each millimeter equals one ten-thousandth of a volt. The pulse rate averaged 68, the *P* wave was present in every case, there was no auriculoventricular or intraventricular block, and no definitely abnormal axis deviation was found. The *P–R* interval was less than 0.18 second, except in 1 case where it was 0.20 second. The *Q–R–S* complex in some instances was decreased in amplitude, approaching the "low potential" type and increased as did the *T* wave with thyroid treatment.

Zondek[2, 3] has reported increase in the size of the heart as studied by the Roentgen ray in myxedema and absence of both *P* and *T* waves in the electrocardiogram, the heart size decreasing, except for some widening of the aorta, and the *P* and *T* waves appearing after thyroid administration. He has also reported the same signs in a patient in whom symptoms of myxedema had gradually developed following a wound of the neck with suppuration of the thyroid gland.

ELECTROCARDIOGRAPHIC DATA AND BASAL METABOLIC RATE IN CASES OF MYXEDEMA.

No.	Sex.	Age.	Date.	Electrocardiogram.						Basal metabolic rates, per cent.	Treatment.
				Amplitude in millimeters. Each millimeter = 10^{-4} volt.				Rate.	*P–R* interval in seconds.		
				Lead.	*P.*	*T.*	*Q–R–S.*				
1	F.	54	Nov. 27, 1914	I	Flat	+0.5	+3	66	0.17	−20	Started Dec. 1, 1914; thyroid grs. iss t.i.d.
				II	+1.0	−0.5+1	+7				
				III	+1.0	−0.2	+7				
2	M.	29	Sept. 19, 1919	I	+0.5	+1.0	+3	65	0.16	−28	Had been taking thyroid off and on. Sept. 22, 1919, started grs. v daily.
				II	+2.0	+1.0	+8−2				
				III	+1.0	Flat	+5−2				
			Dec. 3, 1921	I	+1.0	+4.0	+6	80	0.14	+9	
				II	+2.0	+4.0	+16−2			Dec. 19, 1921	
				III	+0.5	Flat	+10−4				
3	F.	34	Feb. 23, 1921	I	+0.5	+1.5	+12	80	0.18	−28	Thyroid started Feb. 25, 1921.
				II	+1.0	+0.5	+11				
				III	+1.0	−1.0					
			Mar. 4, 1921	I	+1.0	+2.5	+18	80	0.16	−11	
				II	+1.0	+2.0	+18				
				III	+0.5	−1.0	+4				
			Mar. 12, 1921	I	+0.5	+2.5	+12	90	0.17	+3	
				II	+1.0	+3.0	+19				
				III	+0.5	Flat	+7−2				
			Mar. 26, 1921	I	+0.5	+3.0	+11	80	0.15	+1	
				II	+1.0	+4.0	+21				
				III	not done.						
			April 23, 1921	I	+0.5	+3.0	+11	60	0.16	+1	
				II	+1.0	+3.0	+22−5				
				III	+0.5	Flat	+5−3				
4	M.	30	May 16, 1921	I	+0.5	Flat	+5	56	0.18	−20	Hyperthyroid Oct., 1915, B. M. R. +78; 6 Roentgen-ray treatments. Thyroid grs. ivss daily, started May 16, 1921.
				II	+1.5	+1.0	+6				
				III	+1.0	+1.0	+2				
			June 1, 1921	I	+0.5	+1.0	+5	68	0.16	−8	
				II	+1.5	+2.5	+9				
				III	+1.0	+1.5	+4				
			June 13, 1921	I	+1.0	+2.0	+6	70	0.16	−13	
				II	+2.0	+2.0	+12				
				III	+1.0	Flat	+6				
			Sept. 19, 1921	I	+0.5	+2.0	+5	56	0.17	−1	
				II	+2.0	+2.0	+11				
				III	+1.0	+1.0	+5				

			Jan. 4, 1922	I	+1.5	+4.0	+9	75	0.15	+2	
				II	+3.0	+4.0	+15				
				III	+2.0	+1.0	+9				
5	F.	..	Aug. 22, 1921	I	Flat	Flat	+6	50 auricular premature beats.	0.15	−35	
				II	+1.0	Flat	+4 −2				
				III	Flat	Flat	−4				
			Oct. 31, 1921	I	Flat	Flat	+2	70	0.15	−13	
				II	+0.5	−1.0	+2 −6				
				III	+0.5	−1.0	+2 −7				
6	F.	53	Jan. 23, 1921	I	+0.5	Flat	+6	80	0.16	−27	Thyroid grs. iss b.i.d., started Jan. 22, 1921.
				II	+1.5	Flat	+5				
				III	+1.0	Flat	+1				
			May 2, 1921	I	+1.0	+1.0	+8	80	0.15	−8	
				II	+2.0	+2.0	+10 −2				
				III	+1.0	+0.5	+1 −4				
			Nov. 9, 1921	I	+1.0	+3.0	+12	75	0.17	−18	
				II	+2.0	+3.0	+9 −3				
				III	+1.0	Flat	+2 −7				
			April 24, 1925	I	+1.0	+4.0	+15	80	0.17		
				II	+3.0	+5.0	+10 −3				
				III	+2.0	+1.0	+1 −5				
7	M.	56	June 14, 1921	I	+0.5	−0.5	+7 −3	75	0.18	−33	Thyroid grs. vi daily, started June 14, 1921.
				II	+0.5	+0.5	−3				
				III	+0.5	+0.5	−6				
			Sept. 21, 1921	I	Flat	Flat	+4 −3	100	0.19	−19	
				II	+1.0	Flat	−3				
				III	Flat	+1.0	+2 −10				
			Nov. 21, 1921	I	+1.0	+2.5	+15 −5	80	0.17	−18	
				II	+1.0	+1.0	+3 −4				
				III	+1.0	−1.0	+2 −12				
			Dec. 19, 1921	I	+0.5	+2.5	+15 −2	95	0.16	−8	
				II	+1.0	+1.0	+3 −4				
				III	+0.5	−1.5	+2 −13				
8	F.	53	Jan. 24, 1923	I	Flat	Flat	+4 −2	70	0.19	−34	Thyroid grs. v b.i.d., started Jan. 27, 1923.
				II	+0.5	Flat	+2				
				III	Flat	Flat	−3 +2				
			Jan. 29, 1923	I	Flat	−1.0	+7	86	0.19	−25	
				II	+1.0	Flat	+3				
				III	+0.5	+1.0	−2 +2				
			Feb. 6, 1923	I	+0.5	+1.0	+7	100	0.18	−18	
				II	+0.5	+1.0	+5				
				III	+0.5	+0.5	+3				
			Feb. 13, 1923	I	+0.5	+1.0	+9	90	0.17	−12	
				II	+0.5	+1.0	+10				
				III	+0.5	+0.5	−3				

ELECTROCARDIOGRAPHIC DATA AND BASAL METABOLIC RATE IN CASES OF MYXEDEMA.—(*Continued.*)

No.	Sex.	Age.	Date.	Electrocardiogram.						Basal metabolic rates, per cent.	Treatment.
				Amplitude in millimeters. Each millimeter = 10^{-4} volt.				Rate.	*P-R* interval in seconds.		
				Lead.	*P.*	*T.*	*Q-R-S.*				
			Feb. 27, 1923	I	+1.0	+1.5	+8	85	0.15	+2	
				II	+0.5	+2.0	+6				
				III	−0.5	+1.0	Flat				
			April 10, 1925	I	+0.5	+2.0	+8	64	0.16	−4	On thyroid grs. iii daily.
				II	+1.0	+3.0	+10				
				III	+0.5	Flat	−4				
9	F.	44	Jan. 26, 1923	I	+1.0	−1+1	+4	80	0.15	−34	Thyroid grs. ix daily, started Jan. 26, 1923.
				II	+1.5	−1.0	+8				
				III	+1.0	−1.0	+6				
			Jan. 29, 1923	I	+1.0	+1.0	+5	88	0.16	−20	
				II	+1.5	−1.0	+8				
				III	+0.5	−1.0	+3				
			Feb. 3, 1923	I	+1.0	+2.0	+7	100	0.17	−12	
				II	+1.0	+2.5	+13				
				III	+0.5	Flat	+7				
			Feb. 12, 1923	I	+1.5	−1+2	+13	130	0.14	−4	Died Feb. 28, 1923.
				II	+1.5	+2.0	+13				
				III	+1.5	+3.0	+11				
10	M.	47	April 4, 1924	I	+0.5	Flat	+3	80	0.16	−18	Thyroid started March 29, 1924.
				II	+1.0	Flat	+7−2				
				III	+0.5	Flat	+2				
11	F.	42	April 23, 1924	I	Flat	−0.5	+9	70	0.14	−37	Thyroid grs. viiss daily, started April 22, 1924.
				II	+1.0	Flat	+9				
				III	+0.5	+0.5	+1				
			May 3, 1924	I	+0.5	+1.5	+12	90	0.16	−8	
				II	+2.0	+2.5	+17				
				III	+1.5	+0.5	+6				
			Mar. 13, 1925	I	+0.5	+1.0	+9	60	0.16	−27	Taking gr. i daily past six months, started grs. vi daily March 13, 1925.
				II	+2.0	+1.5	+9				
				III	+1.0	+1.0	+2				
			Mar. 27, 1925	I	+0.5	+2.0	+9	90	0.16	−7	
				II	+3.0	+4.0	+13				
				III	+2.5	+1.0	+4				
12	F.	24	Dec. 11, 1923	I	+1.0	+3.0	+8−2	70	0.19	−32	Thyroid grs. xx, started Dec. 16, 1923.
				II	+1.5	Flat	+20				
				III	+0.5	−2.0	−2+19				

12	F.	24	Dec. 11, 1923	III	+2.5	+1.0	+8−2	70	0.19	−32	1923.
				I	+1.0	+3.0	+20				
				II	+1.5	Flat	−2+19				
				III	+0.5	−2.0					
			Dec. 17, 1923	I	+0.5	+3.0	+7−3	65	0.19	−16	
				II	+1.0	+1.0	+20				
				III	+0.5	−2.0	−2+17				
			Dec. 22, 1923	I	+1.0	+2.0	+9−2	110	0.18	+3	
				II	+2.0	−1.0	+20				
				III	+1.5	−3.0	−2+20				
			Dec. 24, 1923	I	+1.0	+2.5	+10−2	90	0.2	+11	
				II	+2.0	+2.0	+23				
				III	+1.0	−1.0	−3+19				
			Jan. 9, 1924	I	+1.0	+3.0	+9−2	80	0.18	−7	
				II	+2.0	+4.0	+22				
				III	+1.0	Flat	−2+17				
			Feb. 29, 1924	I	+1.0	+3.5	+10	80	0.17	+8	On grs. iv daily; stopped thyroid July, 1924.
				II	+1.5	+4.0	+20+				
				III	+1.0	Flat	−2+13				
										−42	Started March 20, 1925 on grs. iss t.i.d.
			Mar. 27, 1925	I	+0.5	+3.0	+8−1	54	0.18	−28	
				II	+1.0	+2.0	+19				
				III	+0.5	−1.0	−2+15				
			April 25, 1925	I	+1.0	+4.0	+13	75	0.18	−2	
				II	+1.5	+3.0	+22				
				III	+0.5	−1.0	+12				
13	F.	41	Feb. 27, 1925	I	Flat	Flat	+4−3	60	0.17	−28	Thyroid grs. iv daily.
				II	+0.5	−1.0	+6−3	auricular			
				III	+1.0	Flat	+7	premature beats.			
			April 28, 1925	I	+0.5	−1.0	+5	75	0.18	−6	
				II	+1.5	−1+1	+10−3	auricular			
				III	+1.5	Flat	+8	premature beats.			
14	F.	38	April 10, 1925	I	+1.0	+0.5	+3−3	90	0.18	−24	Thyroid started April 22, 1925, grs. ix daily.
				II	+1.0	Flat	−2				
				III	Flat	Flat	−2+2				
			April 28, 1925	I	+1.5	Flat	+3−3	100	0.18	−18	April 28th, grs. vi daily.
				II	+1.0	Flat	+2				
				III	Flat	+0.5	−3+3				
			May 7, 1925	I	+1.0	Flat	+5	75	0.17	−15	
				II	+2.0	+1.5	+4				
				III	+1.0	+1.0	−4+4				

Fahr[4] has recently reported cardiac dilatation in 4 cases of myxedema with marked diminution in size after treatment. Also the electrocardiogram showed diminution of the amplitude of the *T* wave which became higher after medication. However Willius and Haines,[5] in a study of 162 cases of myxedema, failed to find any appreciable dilatation in most of the cases although they did obtain abnormal electrocardiograms.

One of us[6] has recently reported the study of the electrocardiogram in cretinism, another type of hypothyroidism. In all of the 8 cases examined the *T* wave in Lead II was below normal. In the 3 cases who were examined again after thyroid administration the *T* waves had increased in amplitude and the *Q–R–S* waves also showed higher potential difference.

Summary. Our 14 cases of myxedema (see table) showed consistently a low *T* wave in Lead II before treatment with increase in positive amplitude after treatment. Thus there is a distinct parallelism between the *T* wave of the electrocardiogram and the basal metabolic rate in hypothyroidism (Figs. 1 and 2).

In addition, there is a general decrease in potential of all electrocardiographic deflections in all leads in myxedema, with increase after treatment. This same so-called "low potential" in all leads is found in one other condition, that of myocardial exhaustion due to serious coronary sclerosis. This fact is evidence that the heart action is sluggish during myxedema in accord with the recent finding of Einthoven that the electrical and mechanical expressions of muscular activity are not only synchronous but also tend to be parallel in degree. The *T* wave in Lead II may also be lowered by digitalis; but the "digitalis *T*" is somewhat different from the "myxedema *T*" or the "myocardial weakness *T*," the deflection being more often diphasic, particularly with the *S–T* interval inverted.

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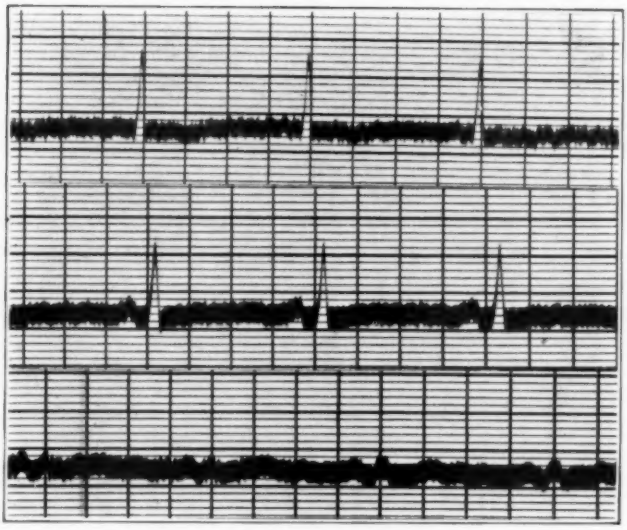

FIG. 1.—Electrocardiogram (Leads I, II and III) of Case 11, on April 23, 1924, when basal metabolic rate was −37. Note low amplitude of the *T* wave, and also of the *P* wave in all leads. (See Table.) Time interval = 0.2 second. Potential difference : 1 mm. = 10^{-4} volt.

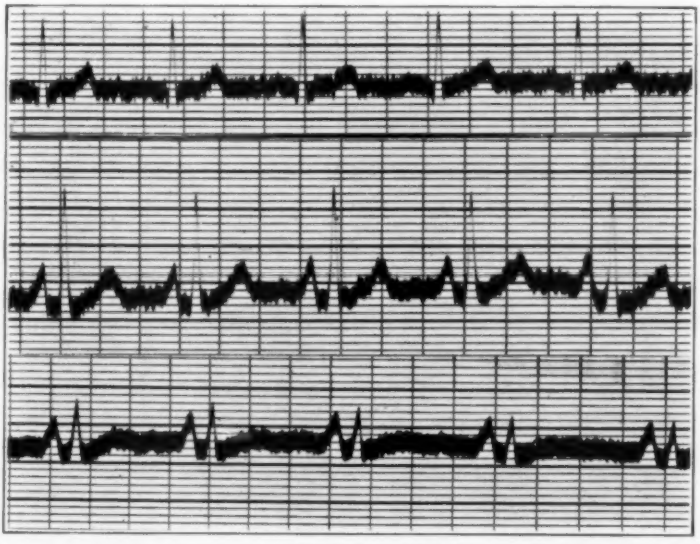

FIG. 2.—Electrocardiogram (Leads I, II and III) of Case 11, on March 27, 1925, when basal metabolic rate was −7. Note increase in amplitude of the *T* and *P* waves in all leads and of *R* in Leads II and III. (See Table.) Time interval = 0.2 second. Potential difference : 1 mm. = 10^{-4} volt.

MEGACOLON: A RÉSUMÉ OF THE LITERATURE AND REPORT OF A CASE. RAMISECTION PROPOSED AS A FORM OF TREATMENT.*

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Literature. The monograph by Finney[1] is the most complete of the many references that I have consulted in my work of studying the literature of this obscure condition. He cites the reports of Parry, in 1825, although Barrington-Ward,[17] in quoting Jayle, says that Runyon in the seventeenth century reported a typical case in a girl aged five years. Billard, in 1829, reported a case in a child, aged six days, in which the lower part of the small, and all of the large, bowel were thickened and sclerosed. These were followed by Ebers, in 1836, and in 1842 von Ammon reported 2 cases—one, a child who died shortly after birth, and another, a fetus at about the seventh month. After these came other cases, reported by Oulmont, in 1843, Banks, Bunfer and Favalli, in 1846, Little and Galloway, in 1850, Gay, in 1854, Henock, in 1861, and in America by Lewitt, in 1867, and Jacobi, in 1870. Then come Barth, Peacock, Gee, Brostow, Morris Fütterer, Middeldorf, Cheadle, Gauma and others.

It is only fair that here attention be called specifically to the report made on May 27, 1886, by a prominent Philadelphia clinician who is still living—Dr. William E. Hughes[2]—which was published in 1887, before Hirschsprung produced his monograph describing this malady which bears his name. Hughes reported the autopsy findings in a boy, aged three years, dying during an attack of acute colitis. The colon had a capacity of 14 pints (7000 cc.) The gut wall was hypertrophied, and the dilatation while present throughout the colon was marked in the sigmoid region where a diameter of 4 inches was noted.

In 1888 Hirschsprung[3] published his monograph which bears the date of 1886 as the time of writing. He reported 2 cases which during life presented symptoms of constipation and meteorism without signs of stenosis of the gut tract. The first case died at eleven months of progressive cachexia, and the second case died at seven months of multiple ulcerations of the colon. Each case exhibited dilatation of the colon with hypertrophy of the bowel wall. Later 2 more cases were added, making 4 in all.

The case reported by Formad,[4] in 1891, is of interest because it is frequently referred to in the literature and because of the extreme size of the colon, also because of the age, twenty-nine years, to

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which the patient survived with such a gross deformity. Formad stated the size of this man's colon was that of a cow's, and after removal of its 40 pounds' of contents the weight of the colon was a little under 7 pounds. The rectum was normal and the greatest dilatation was found in the sigmoid, although the whole colon was enlarged even to the cecum, which was the least enlarged of all portions. Throughout the whole extent of the colon the wall was found hypertrophied, but there was an anomalous arrangement of the circular and longitudinal musculature and the longitudinal bands were absent. The skeletal muscles were atrophied, and there was complete absence of all fatty tissue even to the omentum. Death occurred suddenly while the man was attempting to defecate. The exact cause of death was not stated by Formad.

Genersich, Demme, Walker and Griffith later reported similar cases, and when Mya,[5] in 1894, added 2 cases, his review of the literature showed a total of 9 cases, although actually there were more cases on record at that date. One of Mya's cases which died during an attack of acute enterocolitis, exhibited ulceration of Peyer's patches.

Formad refers to a few interesting cases. Gruber reported a sigmoid 4 or 5 inches in diameter. Little and Galloway reported a case in which the transverse colon had a diameter of 6 inches and the sigmoid varied from 12 to 20 inches in diameter. Peacock's case had a colon capacity of 15 quarts, and the sigmoid varied from 6 to 8 inches in diameter. Cruveilhier reported a case with the colon the size of a horse's great gut, and one with a diameter of 14 inches.

In 1893 Osler[6] reported 2 cases of marked constipation without fecal impaction or rectal or anal obstruction. He takes pains to remark, however, that Dr. Halstead, who examined 1 of these cases, thought that the sphincter was tight, although Osler himself did not agree to this. Marfan, Treves, Concetti, Fenwick, Fritz, Richardson, Eserich, Frommer, Duval, Kredel, Cheinisse, Perthes, Bing, Pfisterer, Danzinger, Löwenstein, Ito and Sayesima followed with case reports, so that a total of 206 cases was found in January, 1908, when B. W. A. Fisher and Finney[1] made their exhaustive review of the literature.

In the interval of the following seventeen years many cases have been collected, so that the literature of today is quite profusely supplied with reported cases, and with statistical reports on the results of treatment by either the medical or the surgical avenues of approach.

Reference may be made, for instance, to Hubbard,[7] L. W. Johnson,[8] P. P. Johnson,[9] Beath,[10] Matthews,[11] Rogers,[12] Drueck,[13] Shaine[14] and Porter.[15] Neugebauer[16] reported a series of 169 cases in 74 of which the sigmoid alone was involved. Barrington-Ward[17]

did necropsies on 19 cases and found the rectum involved in a few of them. Duval[18] studied 59 cases. Löwenstein[19] reports 44 surgical cases and 59 medically treated cases; Terry[20] reports 110 surgically treated cases. It is to be understood that these cases may overlap, in a measure, for each man has collected the cases, many of which had already played a part in previous statistical studies. However, the cases reported are many when taken in the aggregate. The nearest estimate to the incidence of this condition is that given by Fenwick,[21] who, in a review of 30,000 necropsies in the London Hospital for Sick Children, found only 3 cases—1 case in every 10,000.

Etiology. Many theories have been advanced to explain the etiology of this condition developing in the first year of life, or even during the baby's intrauterine life. A survey of the following list of causes advanced by Barrington-Ward[17] and quoted by Drueck,[13] Bassler,[22] Finney[1] and others reveals the fact that practically every embryonal, histologic, pathologic and physiologic field has been scanned in an endeavor to find the answer and so point to a definite plan of treatment.

The List of Causes. 1. *Mechanical.* Torsion of the sigmoid, because of extreme mobilization as the result of too long mesosigmoid, or because of too great length of the tube itself, or actual blocking of the fecal current from atresia of the anal canal, rectum or sigmoid; imperforate anus (partial type); hypertrophied rectal valves; overdevelopment of O'Beirne's sphincter; the drag of a sigmoid overloaded with meconium acting as a valve, thus preventing its own emptying.

2. *Neuropathic.* Neuromuscular defect, or even a paralysis of a segment of gut; lesion of the sympathetic system; reflex spasm of sphincters due to anal fissure.

3. *Inflammatory.* Chronic colitis leading to changes in the physiology and anatomy of the gut tube through bacterial, chemical and toxic factors.

4. *Congenital.* Anomalous development, that is, congenital dilatation and hypertrophy, as suggested by Hirschsprung.[3] It has been suggested, too, that either of these may be the true congenital anomaly, and the other the secondary result of the primary defect.

To say that a pathologic condition is congenital explains nothing; therefore, I have sought for an explanation of how this hypertrophy and dilatation could be brought about. So, not included in this list, there is another which may be worth considering, and that is a developmental cause. While the embryo is developing its great gut, at the time when by the rapid downward growth of the liver resulting in a marked disproportion between the size of liver and the cavity of the abdomen, a portion of the small gut and all of the large gut is pushed out of the abdomen into the sac. When more nearly normal relations between the size of liver and that

of the abdominal cavity begin to be reëstablished the gut recedes within the peritoneal space, and through growth of the great bowel upward from the sigmoid and rectum, the descending colon, then the transverse, and finally the ascending portions of the great gut take up the positions in which they are found at birth or soon after, and become fixed; in so doing the complete twist from left to right is given to the mesentery of the small bowel as the stomach turns its left side forward. Therefore if there be an anomalous development accounting for this condition of megacolon I think it extremely likely that the condition begins in the very early developmental stage of the embryo—that is, during the first few weeks after gestation. It is just possible, through this displacement and torsion to which the gut with its mesentery is subjected, that the innervation is in some way interfered with, and that the proper balance or reciprocal relationship of the two motor nervous supplies of the gut (the sympathetic and the parasympathetic) is not maintained, and, as a result, function of the colon would be impaired early in intrauterine life.

Pathology. Roughly, 33 per cent of the cases show involvement of the colon in its sigmoid portion alone. A few cases have shown the whole colon to be involved, and rarely the cecum and rectum are enlarged. Many of the surgeons note the lack of development of the external coat of longitudinal fibers which in the normal colon constitutes the longitudinal bands of the great gut. These bands may be absent or poorly defined. The middle coat of circular fibers is usually either well developed or overdeveloped, contrary to what one would expect to find in a dilated colon. The inner coat of muscular tissue may be of normal thickness, as may the mucosa, but this latter usually shows signs of chronic inflammatory changes, such as hypertrophy of its various layers or focal necrosis from minute fissures up to large ulcerated areas, which may extend down through the muscular layers and penetrate the serosa. The serosa is usually blanched when the abdomen is opened if there be a great amount of feces within the colon, due to the pressure on the mesenteric vessels, which are usually long and tortuous, as they lie within the two layers of the mesocolon. The lymph glands are usually hard and may be cystic, and a chronic lymphangitis is frequently evidenced by the thickened mesocolon.

The sigmoid may have a diameter many times its normal size, and the whole colon be greatly lengthened so that it folds and refolds upon itself, sometimes filling the pelvic and greater part of the abdomen and thus crowding the small intestines up under the liver, stomach and spleen.

Symptoms. For every female afflicted with megacolon there are 3 males similarly afflicted. Many of the cases are diagnosed soon after birth, and by far the largest proportion of them before the first year.

The only constant symptoms or signs are: (1) A history of constipation with constant laxative, purgative or enema habit, dating very likely from birth. (2) Abdominal distention. (3) Roentgen-ray findings after a barium enema.

Besides these three cardinal ones there is a mixed array of signs and symptoms which may be present singly or in combination: (1) Muscle atrophy, especially of the abdominal wall, allowing the loops and coils of the bowel, undergoing their peristaltic activity, to be seen; weakness of muscles of extremities. (2) Loss of the subcutaneous fat. (3) Toxic symptoms—headaches, socalled bilious attacks, nausea, vomiting, chilliness, prostration, stupor and lassitude, and irregular fever. (4) Anemia is rather rare, except in the far-advanced cases. (5) Lack of proper development. (6) Because of the impaired mechanics of the gut tube, sleep is apt to be disturbed, and during the day the child is restless, irritable and unhappy. (7) Usually the child will not even try to defecate when placed on the vessel, but "will sit for hours;" the stool in response to enema may be formed and only thumb sized; indeed, not the large massive balls or sausages that one would be led to expect from some textbook descriptions. (8) Palpation may elicit a large mass in the left lower quadrant, but if the mother has been giving good attention to the child, the bowel may be found relatively empty; it is not necessary to have fecal impaction in megacolon; but always the bowel is distended with gas and is easily compressible without resulting pain. (9) There has been little attention paid to the tonicity of the anus in the reported cases, but when this finding has been recorded a spastic state or hypertonicity would seem to be the rule. It is quite likely that hypertonicity will be found more frequently if looked for during life. Finney states that the anus is usually normal, but I believe this observation relates to the examination of the dead sphincter, so naturally a functional disturbance would not be found.

Treatment. Hubbard[7] gives a good statistical review of the comparisons to be made between treatment given by the medical and the surgical methods. Duval[18] showed that the mortality in those cases treated medically is 74 per cent, and in those treated surgically 34 per cent. Löwenstein[19] has worked out two sets of statistics. He first reported 44 operative cases, of which 21 (48 per cent) died, 2 were unimproved, 7 were improved and 15 (34 per cent) were cured. Of 59 cases treated medically, 39 (66 per cent) died, 9 were improved, 4 were unimproved and 7 (12 per cent) were cured. Finney,[1] in commenting on these figures, concludes that the surgical mortality rate is two-thirds that of the medical, and that the surgical recovery rate is three times as great as the medical. Terry[20] collected 110 surgically treated cases, and records that there were 82 (74 per cent) recoveries and 28 (26 per cent) deaths. Neugebauer[16] collected 133 medically treated cases,

and reported cures in less than 2 per cent. He states that in selected cases the two-stage operation (anastomosis and, later, resection) has given as high as 90 per cent recoveries.

So the statistical evidence is plainly against the expectant medical plan of treatment, yet one must remember that it is just possible that many of the surgically treated patients may have died of various causes since their discharge marked "cured" was written; while all medical cases may have been scored up against "death from megacolon," even though these deaths occurred later from intercurrent disease. Even though these statistics may be misleading, I believe that in the majority of cases treatment eventually will have to be of a surgical type. It is hard to bring one's self to condemn these little patients to the vicious colon resection operation while there is the slightest possibility of helping them in some other way, and that is one reason why I am proposing ramisection as outlined under "Theoretical Discussion" of this paper.

In a medical way I believe the best results are to be obtained through the judicious use of sine-wave electricity to the abdomen and by preventing the possibility of toxemia from intestinal decomposition by the removal from the diet of all food containing animal protein, excepting milk and its products, such as cheese and butter; but even milk may have to be withdrawn if it be found that it disagree. Bacillus acidophilus and lactose should be given, watching the effect of the latter in producing distention through fermentation. The starches are almost universally condemned by most clinicians, but I believe they are usually well borne, even when given in excess for the purpose of building up the caloric requirements of the diet after the withdrawal of the animal protein—the chief offender through decomposition in the torpid great gut.

Laxatives must be given to procure some motility. Sodium sulphate in ½-dram doses, or less, night and morning, is probably the best because of its tonic action on the bowel musculature as contrasted with the relaxing effect of magnesium sulphate, which is not well borne. The mineral oils are bad because a lubricant is not called for in this condition, and because there is always the possibility of impairing the assimilation of food through its use. One cannot afford to take this risk in these patients for they are usually far below normal and must be built up through sufficient food intake, with olive oil and cod-liver oil, preferably fortified by the vitamins. Yeast is probably a poor form of medication in these cases because of the possibility of increasing the distention, which is sufficiently embarrassing to the patient's comfort under the best of conditions.

The wearing of an elastic binder, made to fit by careful measurement, is advisable; but, as a rule, it is a procedure difficult to follow out, because adjustments have to be made frequently to accord with the varying diurnal dimensions of the abdomen. All the usual

hygienic measures should be adopted to benefit the child generally. Exercise, especially, should be encouraged. Enemata should be given daily to aid in the emptying of the sigmoid. Normal salt solution is the best, but 5 to 10 per cent glucose, or 5 per cent sodium bicarbonate or sodium sulphate solutions may be used.

Lastly, medicines may play a very helpful part. Nux vomica is perhaps the most useful one for its stimulating effect on the vago-pelvic (bulbosacral or parasympathetic) nerve supply of the large gut, as well as for its tonic effect on the musculature. Adrenalin is contraindicated if our conception of an overactive sympathetic supply be correct. The use of pituitrin has been advised by Berger,[32] who reports good results from its administration in 10-drop doses four times a day, by mouth. Arsenic and iron (preferably one of the albuminoid forms) may be found extremely useful as reconstructives.

By these measures some of these sad little patients may be helped along sufficiently to make life a pleasure rather than a burden to them and their parents, and if, by following them, we do not effect a cure, we may have the satisfaction of knowing that at least we have made conditions better, and that the ability of the patient to withstand the serious and dangerous operation of resection—if that be the type of operation chosen—is greatly enhanced.

Case Report. G. L. C., 3d, male, aged three and a half years, was referred to me on April 17, 1923, by Dr. George T. Tracy, with a chief complaint of irregular bowel movements, abdominal distention and passing of flatus. The family history is negative, except for atonic constipation in the mother and the maternal grandmother. There are two younger sisters and one older brother, normal in every way except for hypertrophied tonsils.

Past Medical History. The child was born naturally; weighed a little over 8 pounds. At birth there were already erupted the two lower central incisors, which were immediately removed by the doctor in attendance. He was breast fed for six months, and then placed on modified milk. Almost from the day of his birth the bowel movements have not been normal. Laxatives, enemata and cathartics have been resorted to constantly since his first year to produce long, thin, cylindrical bowel movements. He has suffered none of the infections of childhood, but has had frequent socalled bilious attacks—bad color (sallow and pale) prostration and crossness. At all times he has been easily chilled by the slightest exposure, so that he actually feared the cold; he has had very little inclination toward exercise, and never cared to run about and play with the other children.

Ten months previously (July, 1922) a diagnosis of anal fissure, with very marked contraction of the sphincter, was made by

Dr. J. H. Allen. He made an uneventful and prompt recovery on local application of 2 per cent silver nitrate.

Present Illness. There had been no marked change from his previous condition, except that recently the child had suffered with more frequently recurring bilious attacks. The mother had noticed that the constipation was more pronounced, requiring a greater amount of laxative medicine and, occasionally, oil rectal injections because of the hardness (in consistency) of the fecal movements. The mother had noticed, too, that the distention of the abdomen had increased during the last six months, and was greater, especially after she had given the patient white bread and potatoes. Under the direction of Dr. Tracy the child's diet had been properly regulated, so that it was well balanced, and contained more than the usual amount of foods, insuring a sufficient cellulose residue. Much experimenting had been done in administering milk and its modifications with the usual diet, and in withholding it, without producing any change in the patient's symptoms.

Physical Examination. The boy weighed 32 pounds, and the mother felt that he had gained very little in weight, if any, within the past six or eight months. His skin was pale, but the mucous membranes were of a good red color, so that anemia was not striking, considering his blonde complexion. The scleræ were of the usual healthy pale blue color, and the pupillary reactions were normal. The nose and ears were negative. The tongue was clean and the tonsils, also, to compression testing. The usual number of teeth—twenty—had erupted. A space which should have been filled by the lower central incisors (which were removed immediately after birth) had not been encroached upon by the eruption of the lateral incisors, and this space caused a lisp in the child's articulate speech, which was otherwise normal, and seemed to denote that his mentality was up to the standard norm for his age. The heart and lungs and mediastinum were negative to the usual physical test procedures. There was no adenopathy, and the bony development was normal except for a suggestion of a Harrison's groove, because of the marked distention and protrusion of the abdomen.

The abdominal wall was very thin, and the recti abdominalis could not be pinched up between the examining fingers. The umbilicus protruded slightly. There was no hernia evident at the umbilicus, or inguinal rings, which was surprising considering the thinness of the abdominal wall, for loops and coils of the small intestine undergoing peristaltic movement were easily visible over the dome of the abdomen. Percussion gave deep tympany in both flanks and, to a less marked degree, across the upper abdomen. The abdomen could be easily compressed by the palpating hand, and no masses were felt, especially along the course of the descending colon and sigmoid.

The musculature of the extremities was underdeveloped, but was not wasted. There seemed to be more than the normal moderate degree of lordosis seen in children, but because of the abdominal protrusion this could not be accurately estimated. The umbilical reflex was absent, the cremasteric was doubtfully present and the patellars were normal.

Examination of the anus, while feared by the little patient —evidently because of his fairly recent proctologic experience— proved to be painless, but the anal muscle throughout its depth was tonically contracted, so that considerable force had to be exerted to intrude the anointed index finger tip within the anal canal. No linear induration could be palpated at the site of the former fissure, so that it did not seem possible that scar tissue formation could be a factor in producing the apparent overtonicity of the muscle. The anus was dragged easily to the posterior and to both lateral directions without the production of pain. The finger was introduced to its full length, and no feces was found within the rectum, nor were thickened rectal walls palpated, nor could a mass in the left lower quadrant be palpated bimanually. More relief was experienced, I imagine, by the examiner than by the patient on withdrawing the finger, for it was blanched by the constricting pressure of the hypertonic anal sphincter.

Since the purpose of this paper is to serve as a text, and to call to the attention of diagnosticians the possibility of the existence of megacolon without large colonic collections of feces, let me say that I did not call this a case of Hirschsprung's disease. The evidence did not seem sufficient to warrant such a diagnosis, nor was I willing to subject this patient to the danger of a colon resection, even though it was known that marked atony and dilatation of the colon existed. There was the marked atrophy of the abdominal musculature to be considered, for it was possible that this was one of the obscure types of congenital asthenia (amyotonia congenita). Then the tonically overactive anal sphincter could have explained the apparent constipation. It was thought wise to place the child on tonic treatment, to encourage the development of the abdominal muscles by exercise and massage, and to endeavor to procure some relaxation of the sphincter by the daily insertion of the finger to stretch and iron out the muscle; but little was hoped for from this procedure—as little as from the use of dilators where there is no scar-tissue deposit.

On the return of the patient in October, 1923, after the family's return from Maine, whence they had gone shortly after his first visit, I was shocked on observing his condition. He had gained only ½ pound (weight, 32½ pounds); he walked with a shuffling gait, sliding the feet along without lifting the toes, and so, frequently falling. He could walk up only two steps of the stairs

without a prolonged rest, and this was possible only when he threw his body forward and maintained his balance by placing his hands on his knees as he labored to step up. The lordosis was decidedly marked, and the angulæ scapulæ stood out and were of the alar type. The shoulders and pelvic muscular groups were markedly wasted, as were the palmar and thenar interossei. He could not climb up on the examining table from a stool, and, when aided, fell upon his face on the table top, his arms to the side, powerless to elevate his torso by his weakened shoulders and arm muscles. When placed upon his back he was unable to rise to a sitting posture even when allowed the use of his hands. The abdominal muscles were as thin as before, and the anus was still rigid. There had been no improvement in his bowel function.

He was seen by Dr. William G. Spiller, who ruled out muscular dystrophy and made a diagnosis of muscular atrophy concomitant with megacolon.

Dr. Spiller reported: "November 3, 1923: The boy moved all four limbs freely. It seems very doubtful to me whether he has atrophy of the shoulder girdle and interossei muscles. He does not have the 'loose shoulder' and 'winged scapulæ' so common in muscular dystrophy. His patellar reflexes also are very prompt, even probably a little exaggerated, which would be unusual in progressive muscular dystrophy. His biceps and triceps reflexes are not distinct on either side. He can rise from the floor without assistance, and has only a little tendency to 'climb on his thighs' to assist himself in elevating his trunk. The distention of the abdomen is remarkable, and when he stands he has some tendency to lordosis; this seems to me to be secondary to his distended and protruding abdomen. He has difficulty in going-upstairs. His sensation for pinprick is good. It is difficult to test other forms of sensation in a child four years of age. Tonicity of limbs when they are moved passively seems good. The boy is weak everywhere but he has no local atrophies, and the weakness is such as could come from some systemic disturbance with malnutrition. The case does not appear to me as one of amyotonia congenita. If this case be one of progressive muscular dystrophy it is without characteristic findings and could only be in the early stage. It does not appear to me as one of muscular dystrophy. The condition is suggestive of megacolon."

The roentgenologic examination by Dr. Willis F. Manges showed megacolon.

Dr. Manges reports: "November 6, 1923: There is undoubtedly a megacolon present. This was not only apparent from the large amount of gas present before the injection but was also verified by the injection of barium. I injected only as far as the splenic flexure and I stopped at this point for the reason that it seemed to me that the child was beginning to have some little

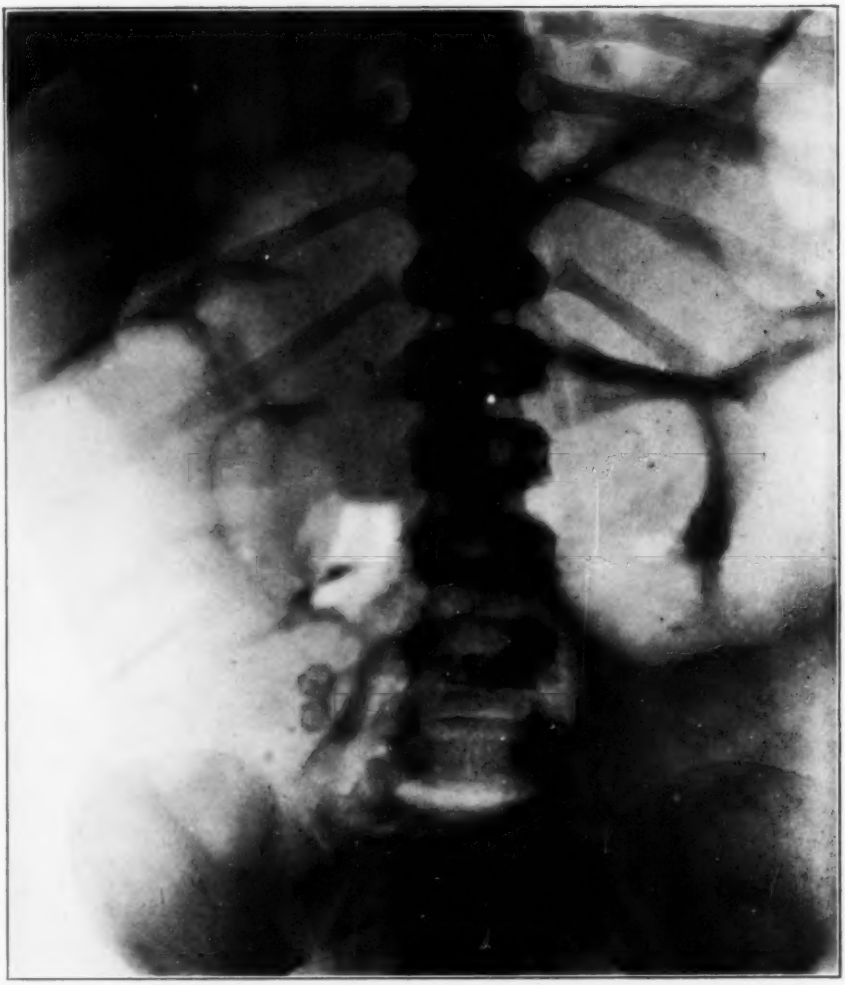

FIG. 1.—Case G. L. C. Exposure made in November, 1923, showing the colon under natural conditions before barium enema had been administered. Note the distention of the bowel with flatus, the absence of the haustral markings and the refolding of the gut.

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FIG. 2.—Case G. L. C. Roentgenogram made in November, 1923, after barium enema. Only the rectum, sigmoid and ascending portions of the colon have been distended by the barium, which did not go beyond the splenic flexure. Note the refolding, the absence of haustral markings, and the enormous capacity of the gut.

FIG. 3.—Case G. L. C. Exposure made in February, 1924. Filling of the entire colon as far as the cecum. Note reduction in capacity of the gut, but still the refolding and absence of haustra.

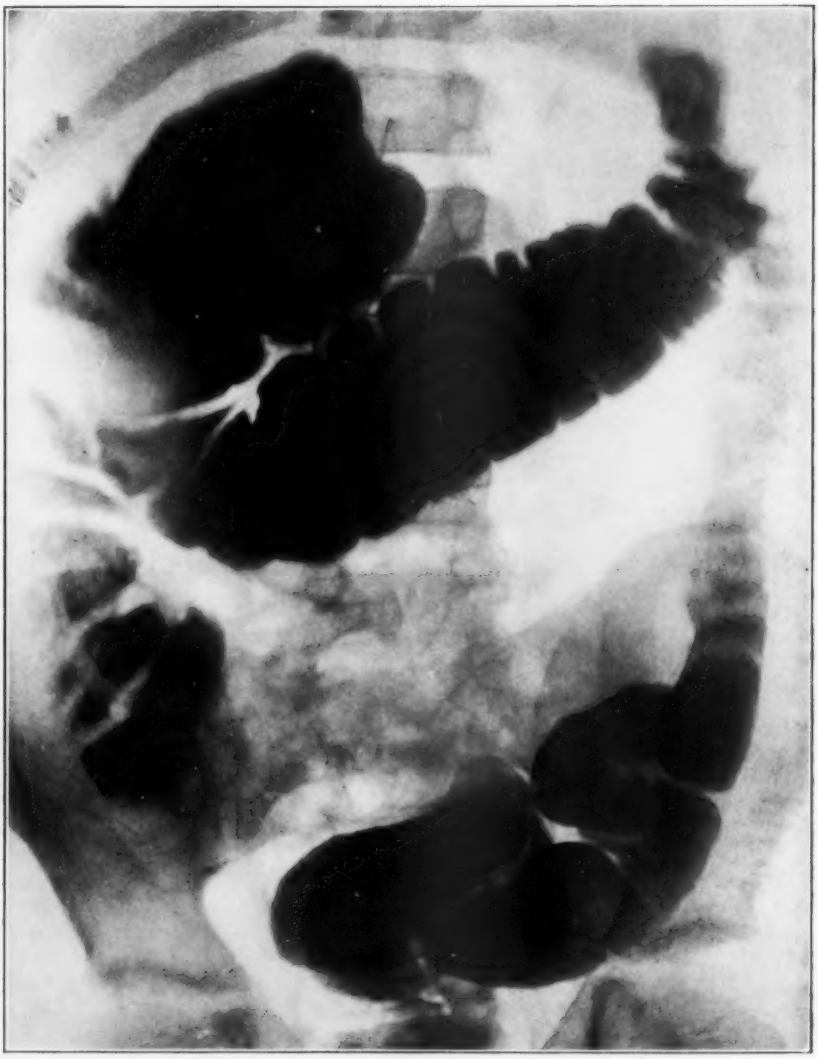

FIG. 4.—Case F. C. L. From another patient aged twelve years, with dilatation of the ascending, and the right half of the transverse portions, of the colon. The descending portions, as well as the sigmoid and rectum, are normal as to size and tone. Comparison should be made between the size of this sigmoid in a child of twelve years and that in the other roentgenogram of the case aged three years reviewed in this article.

embarrassment in breathing. I think it is important, however, to note that the colon was entirely empty of fecal matter when he came to me for study."

Immediately following the Roentgen-ray examination there was great pain and distress, and embarrassed respiration because of the enormous distention of the abdomen. He was unable to empty the bowel voluntarily, even though the intraäbdominal pressure was very great. A rectal tube was inserted and large volumes of gas with over 1500 cc. of liquid feces and barium solution were drained off, the latter part of it aided by pressure of the hand on the now flaccid abdomen. The hypertonic anal sphincter seemed to be the cause of the obstruction, for as soon as the tip of the tube entered the rectum the contents gushed through.

Subsequent Course and Treatment. He was placed on sodium sulphate, ½ dram night and morning; increasing doses of tincture of nux vomica; acidophilus milk; meat-free and fairly high-starch diet; sine-wave electricity to the abdomen and general massage. To move the bowels the plan suggested by Dr. Horace Soper, of St. Louis, was followed. This was the injection of 2 ounces of the following solution: Saturated magnesium sulphate solution, 1 part; saturated sodium sulphate solution, 1 part; warm water, 2 parts. This plan of treatment insured a copious bowel evacuation each day. At the end of a week the patient had gained sufficient strength to permit the administration of nitrous oxid and oxygen anesthesia, while a search was made for a possible anal fissure. None was found. Divulsion of the anal muscle was then attempted, but not accomplished because under the anesthetic the muscle could be stretched to its utmost limit but would not tear. Again it was noted that once the spasm of the sphincter was removed the contents of the rectum and sigmoid were discharged with explosive violence. Within another week the child had his first voluntary bowel movement, and was playing about without exhaustion, going up and down stairs freely. The abdomen was much less distended at all times, and the rectus muscles could now be felt as very thin bands; all his muscles were of fairly good tone.

Cod-liver oil was added to his diet, and a very small amount of meat was allowed twice a week. The sodium sulphate by mouth was stopped and fruit paste substituted for it. By January, 1924, his weight was 35¾ pounds, and this represented a gain of nearly 4 pounds in two months. At times there were small formed, voluntary, finger-sized bowel movements.

In February, 1924, another Roentgen-ray examination was made in an endeavor to check up on the condition of the colon.

Dr. Manges reports as follows: "February 2, 1924: The sigmoid and descending colon, so far as I can tell, permit of the same distention that they did at the former injection. There was,

however, considerably less gas in the colon and I succeeded in getting the barium mixture into the entire colon. The point of greatest dilatation is the lower end of the sigmoid and rectum; then gradually diminishes so that at the cecum the dilatation is not so great—I should say less than half of what it is at the sigmoid."

While there had been a great change in the child for the better—he was robust and played outside for the greater part of the day in the cold, he ate and slept well, and occasionally had an unassisted bowel movement—it was felt that the sphincter was still disproportionately overactive as compared to the activity of the sigmoid. In an endeavor to correct this defect, I asked Dr. Allen to incise the sphincter.

Dr. Allen's report of operation: "March 22, 1924: The muscle was divided on the left side midway between the anterior and posterior boundaries, taking care to make incision at right angles to the fibers of the muscle. The wound was kept open and allowed to heal by granulation; recovery was uninterrupted and function good."

There was, undoubtedly, improvement in the bowel function following the sphincterotomy. Treatment with sine-wave electricity was persisted in, and the abdominal muscles became progressively firmer and stronger. All medicines were withdrawn with the exception of fruit paste, which was required to afford a voluntary bowel movement. But by June, 1924, the anus was as tonically contracted as ever.

Since then there have been transient attacks of constipation, but these have always been easily overcome by enemata. Fruit paste is given almost nightly to insure an evacuation, even under the most favorable conditions. The child now weighs 40 pounds, is sturdy and physically the most active of all the children of this family; while he is still constipated, the original condition has been greatly improved, but is decidedly not cured.

Theoretical Discussion. Some form of operative procedure will probably be necessary to bring about a complete cure in many cases of megacolon. There are many types of operation to choose from—colostomy, colon plication, colopexy and enteroanastomosis with or without resection. Finney[1] favors the two-stage operation of ileosigmoidostomy: (1) The anastomosis, and (2) the resection of the colon.

I should like here to offer a suggestion (first brought to my attention by Dr. George Dorrance) as to a form of surgical treatment of megacolon which may be rational—the operation of ramisection or sympathetic ramisectomy, as introduced by Dr. N. D. Royle.[23] Devine[31] has given it some consideration, and by destroying a part of the sympathetic supply of the slow stomach has lessened its emptying time.

The work of Royle and of the late Dr. John I. Hunter[24] has

shown that spasticity in the muscles of a limb, paralyzed through a central or cortical lesion, may be overcome by removing the influence of the sympathetic nerve supply to the limb. This is done by severing the sympathetic fibers, the gray ramus of the several intervertebral or spinal nerves, going to make up either the brachial or the sacral plexus. After thoroughly reviewing the work of these two men, and studying some of the theories of the function of the sympathetic nerve supply of the bowel as propounded by Gaskell,[25] Bayliss,[26] Macleod,[27] Langley[28] and others, the conclusion is forced upon me that in megacolon we have a condition that very closely resembles in its functional aspect spasticity in centrally paralyzed limb muscles. If this be so a similar method of treatment would seem rational. In one of Royle's operations he cut the white ramus (the second lumbar of the right side) and this procedure promptly gave relief from a very obstinate constipation of long standing, without affecting the bladder function.

The sympathetic fibers supplying the bowel are purely motor in function. They originate in the lateral horn of the gray matter of the spinal cord and leave the anterior portion of cord as the white ramus, in company with the voluntary spinal motor fibers, and pass through the intervertebral foramina on either side of the spinal column. On the anterior surface of the body of the vertebræ they form the sympathetic cord, and from this cord there passes back to the intervertebral or spinal nerve, the gray or nonmedullated ramus. This ramus contains the sympathetic nerves to the skin (pilomotor and sweat), the vasomotor (constrictor) and muscular fibers. These sympathetic nonmedullated fibers accompany the spinal nerve to all of its various musculocutaneous distributions. In the muscle its terminations are separate from the end-plate terminations of the motor nerve, and its function is that of maintaining the plastic tone of the muscular fibers, that is, once the muscle becomes flexed through voluntary action, it tends to stay flexed through action of the sympathetic impulses; or, again, once the muscle is extended through voluntary nerve impulse, it tends to stay extended through the constant activity of sympathetic impulses. The muscle tends to maintain this or that position—it tends to stay put—through this sympathetic influence. One can conceive of a lead-pipe spasticity resulting from sympathetic hyperactivity, or even of a cataleptoid state, as spoken of by Sherrington.[29]

It is thought that the function of the sympathetic as far as the bowel, too, is concerned is practically identical with that of the muscles of the extremities; thus, if the bowel becomes distended through feces being pushed down into a certain segment, as the result of intermittent impulses of the parasympathetic nerves (bulbosacral or vagopelvic, enteral or autonomic) then the con-

stantly acting sympathetic impulse tends to maintain this posture of the bowel segment, it tends to maintain the muscular tube in a certain degree of contraction or dilatation until another intermittent motor impulse comes along through the parasympathetics to cause the tube to further contract. In the sigmoid this impulse would come through the pelvic nerves—nervi erigentes—derived from the first, second and third sacral spinal nerves (running directly to Auerbach's plexus in the bowel wall), having the same propulsive function for the colon, or at least for its lower portion, that the vagus (tenth or pneumogastric) nerve has for the upper part of the gut tract. Stimulation of the pelvic nerve produces contraction of the lower colon (sigmoid and rectum) and coincident relaxation of the anal musculature. The sympathetic nerve supply of the sigmoid comes from the abdominal sympathetic chain, through the inferior mesenteric plexus, the hypogastric nerves and the hypogastric and pelvic plexuses. In function, the sympathetics inhibit the action of the pelvic nerve impulses, maintain the sphincter in a state of tonic contraction and keep the bowel musculature in a certain "posture" as regards distention without in any way increasing pressure within the bowel. This was well shown by Masso and Pellacani[30] in the case of the urinary bladder of the dog, which has a similar innervation—that whether it contained 10 cc. or 90 cc. of water the intravesical pressure remained constant, namely, that of 10 cc. when 80 cc. more were added. This was not so, however, for dead bladders. Thus the sympathetic innervation provides for the muscle assuming this or that "posture," and the term plastic tonus has been given by Sherrington to this postural reflex contraction.

So, one can conceive of a sigmoid, or of a colon, having disproportionately functioning parasympathetics and sympathetics, having markedly unbalanced impulses given to it and to its anal gate tending through overaction of the sympathetic supply to become unresponsive, then to dilate and hypertrophy. This condition is found in megacolon. The same overactivity of the sympathetics would cause hypertonicity of the anal sphincter and thus inhibit the power of the pelvic nerve to relax that muscle. This condition was found the cause of the megacolon here reported.

Hunter[24] has shown, as have others, that removal of the influence of the sympathetic nervous system allows for very much more active function of the bowel by withdrawing the inhibition which the sympathetic places on the activity of the parasympathetics. He believes that by ramisection of the first or second lumbar white ramus this can be accomplished.

I shall welcome the views of others on this point, and am hoping for criticism and discussion to be born by this statement.

It is a difficult operation to perform, but in the hands of a careful man it is a possible operation, as Royle has shown, and extremely

safe from a mortality viewpoint as compared with the various bowel anastomoses. This operation appears to me as ideally suited to cases of megacolon, or, indeed, even to the obstinate cases of atonic constipation, and, when the time comes, unless it can be shown that the premises are faulty, and that the conclusions are illogical, I believe that I shall advise that ramisection be done.

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THE TREATMENT OF ABSCESS OF THE LUNG.*

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and

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In a previous communication[1] (two years ago) we reported our experience with pulmonary abscess based upon a series of 60 cases.

* Presented at the meeting of the Association of American Physicians at Washington, May 5 to 7, 1925.

Since that time we have treated 40 additional cases of this disease which has offered the opportunity to extend and to some extent modify the rationale of treatment which we outlined at that time.

The number of cases which have come under our care has impressed us as indicating that this disease is a more common one than is generally recognized and has increased our interest in the problems surrounding its causation, in the hope of contributing to our knowledge of possible methods of prevention. These studies we expect to make the subject of a future communication.

We have also been increasingly impressed with the seriousness of this condition. This is well brought out by a review of the literature dealing with the treatment of pulmonary abscess by various methods of treatment which indicates a mortality varying from 15 to 60 per cent in reported series of material size.[2] The fact that in this new series of 40 cases we are able to report a mortality of only 10 per cent influences us to offer a description of the system of management yielding these results, which are more favorable than any that we have heretofore obtained and also better than any that we have been able to find reported by others.

System of Management. The term "system of management," rather than that of "method of treatment," is used advisedly for the reason that we are impressed by the variability of response of these cases to any given therapeutic method and by the frequent necessity of modifying or combining various methods in order to obtain the best results in any given case. We have found it futile to accept any one method as generally applicable, but in the study of our cases have been able to employ all of the generally recognized methods to more or less advantage. We have, therefore, no new method to suggest, but rather a method of approach which has left us free to apply any or all known methods according to the indications presented.

We believe that this would have been difficult, if not impossible, had we not undertaken this study as a joint problem for internist and surgeon, for this disease lies in that borderline zone of medicine and surgery which presents problems of constant and continuous interest to each. All of our cases have, therefore, received equal and regular supervision from us both and no plan of treatment has been undertaken in any case excepting as agreed upon in joint conference.

We have also found it increasingly important to introduce a third viewpoint into our case studies in that of the bronchoscopist and we have been exceedingly fortunate in having the close coöperation of Dr. John Kernan in this series of cases, who has seen many of them with us and has bronchoscoped several when the indications seemed to demand this procedure.

The system which we have come to adopt is first and foremost absolute bedrest, combined with postural drainage. As soon as the

diagnosis is established, all cases are placed under this regimen and watched very carefully, with special reference to the behavior of the temperature, the amount and character of the expectoration and the changes exhibited in the Roentgen-ray films, which are taken at least once a week. Physical examinations of the chest are, of course, made frequently but yield less valuable information than these other observations.

The progress of each case is studied in joint conference once a week, or oftener if special developments occur, and if the progress is not deemed satisfactory, additional methods of treatment are considered. They are bronchoscopy, operation by incision and drainage or artificial pneumothorax. It is unusual that any of these methods are employed before the expiration of three or four weeks of the more simple medical treatment by rest and posture.

We also consider it important to make Wassermann blood tests in all cases and to employ systematic antisyphilitic treatment in every one which reacts positively. This treatment appears materially to enhance their prospects of cure without radical procedures.

With this general plan in mind it will assist to a better understanding of our specific methods to consider the elements in our system of management separately and to evaluate the importance of each and its relation to the plan as a whole.

Rest. It is only in the past two years that we have come to what we now consider a proper appreciation of the value of prolonged bedrest in the treatment of lung abscess. We were influenced considerably by Pritchard's[3] valuable contribution to this subject and have come to agree very heartily with his conclusions.

During the febrile period bed treatment is obviously indicated and probably universally employed, but in the majority of these cases the fever subsides more or less promptly even with inadequate drainage of pus through a bronchus, and it is quite common to note a consistently normal temperature without a correspondingly satisfactory decrease of cough and expectoration, or of improvement in the character and extent of the lesion as shown by the Roentgen-ray films. Under such circumstances, the general condition of the patient is naturally better and often confinement to bed becomes irksome, but we believe that persistence in bed until the cough, expectoration and Roentgen-ray findings, as well as temperature, all indicate the clearing up of the necrotic process in the lung is most important and will very materially assist the postural treatment in obtaining a socalled medical cure. Moreover, we believe that rest plays a valuable role for many weeks after all symptoms have been absent, especially if the Roentgen-ray densities have not absolutely and entirely cleared. In such cases relapse into acute symptoms may occur even many weeks after all cough and expectoration and fever have disappeared and we have for this reason had several occasions to regret a premature discharge from hospital supervision or return

to the normal activities of life. We therefore advise a prolonged period of weeks or even months of an after cure very similar to that employed in the management of a partially arrested case of tuberculosis, until the last vestige of pathological Roentgen ray shadow has disappeared or what remains may be fairly certainly interpreted as representing a permanent fibroid change.

In this after-cure hard physical work or violent exercise are excluded and rest in the recumbent position is required for considerable periods each day. These are gradually diminished and increasing exercise allowed until a normal degree of active life is attained and a permanent cure is effected.

Postural Drainage. Cough with the expectoration of pus occurs in all cases of lung abscess in which there is a communication with a bronchus. Complete drainage of the abscess may result in this manner and a spontaneous cure thus effected in a limited number of cases. As a rule, the cough, while producing the expectoration of foul pus in large quantities, only succeeds in eliminating the amount which constantly wells up into the bronchi, leaving the abscess cavity itself still completely or partially filled with pus, with consequent increasing necrosis and collateral inflammatory reaction in the lung itself. Certain positions of the body will very frequently aid in the more complete emptying of the cavity by the cough and thus the proportion of cases cured by this natural method of drainage may be materially increased. Patients will themselves frequently note that certain positions increase the amount and ease of expectoration and these observations are often valuable guides to postural treatment.

In general, we invert the patient completely with the head hanging straight down to the floor bending at the waist over the edge of a bed. A twist of the body so as to bring the affected side to a higher level than the opposite one is often desirable. Sometimes lying on the back with the head down, with the body held in position by the bend of the knees is more effective. This can be accomplished by the reverse use of the break of a Gatch bed, or by lying over a stiff chair inverted and placed upon a flat bed. Sometimes the best results are obtained by positions which have no logical explanation as far as the location of the abscess is concerned, and we have been interested to note that upper lobe abscesses are quite as apt to drain by the inverted posture as are those situated in the lower lobes. In any event, considerable time must be spent in patient experimentation with each case to discover the best position for that particular patient.

After this has been determined, this posture is prescribed at regular intervals, usually every three or four hours at first, and is maintained for periods varying from five to fifteen or twenty minutes. The discomfort felt in the head from the inverted position quickly disappears and patients rarely complain of it after the

first day or two. An observant patient soon learns from his own sensations when he needs drainage and the interval and duration of each treatment is modified accordingly.

The effect of this treatment is very striking when successful. The more complete emptying of the cavity gives a complete cessation of cough for hours at a time, allowing a very gratifying relief from the constant and harassing paroxysms which so often mark this disease. The amount of expectoration which is carefully measured and noted for each twenty-four hours, at first very materially increases and then in a few days gradually diminishes until it may entirely disappear in a week or ten days. The fever subsides and the patient is transformed from a miserable and acutely ill person to a comfortable convalescent. Many times these desirable results are only partially obtained and in still other cases no appreciable result in amelioration of symptoms is noticeable. In such cases after adequate trial it is necessary to supplement this treatment by one or the other of the other methods to be later considered.

We are accustomed to persist in this treatment for at least three or four weeks before discarding it, because not infrequently good drainage may be established quite suddenly in cases which have shown no results during the first weeks. In the evaluation of this, as well as all other methods of treatment, the comparative Roentgen ray films are the best single guide.

As already described, absolute bedrest is prescribed in the intervals between the postural treatments.

This combination of rest and postural drainage constitutes our basic method of treatment to be first used in practically all cases and the result obtained affords the point of approach to our consideration of additional methods. In the series of 40 cases here reported it was the only treatment employed in 14 cases, of which 8 were cured and 6 markedly improved.

Bronchoscopic Treatment. Our earlier experience led us to doubt the general applicability of the bronchoscope in the treatment of lung abscess. We were also impressed by the fact that some fatalities occurred and that very frequently it was a most distressing ordeal for the patient.

We have considerably modified our previous point of view in the experience which we have had through the close coöperation of Dr. Kernan in the study of many of our cases. While we cannot share the enthusiasm of some who consider the use of the bronchoscope as the most important method to be first considered in these cases, we do feel that in many it may facilitate drainage when it is not promptly established by the rest and postural plan.

We believe, however, that the possible dangers and discomforts of this method are eliminated only if it is in the hands of a very skillful operator of large experience and mature judgment. We

feel that the occasional bronchoscopist should not attempt the treatment of lung abscess.

That this method in skilled hands is useful and not dangerous in properly selected cases is evidenced by the considerable experience now reported by such bronchoscopists as Chevalier Jackson,[4] Lynah,[6] Carmody,[7] Yankauer,[8] Kernan and others, by the testimony of such thoracic surgeons as Lilienthal and Willy Meyer[9] and by the experience of internists such as McCrae[5] and Funk.[10] They emphasize the importance of early treatment in acute cases and report occasional very prompt cures, often great improvement and in chronic cases amelioration of symptoms with occasional cure.

This has also been our experience but we emphasize the importance of rest and posture as basically important and the use of the bronchoscope, which can only be employed at about weekly intervals, as a most valuable adjunct to this treatment in many cases by helping to establish more prompt and direct drainage.

It is our experience that it is the passage of the tube, combined with suction, which is valuable, and that lavage and the introduction of such medicaments as antiseptics, local stimulants, bismuth and the like, have no value and may do harm. We do not favor bronchoscopy in abscesses situated near the periphery of the lung, it is contraindicated in those not communicating with a bronchus, and is less apt to be successful in lesions situated fairly high up in the upper lobes. It is most useful in abscesses situated near the main bronchi, especially those in the lower lobe, but it is to be noted that it is just in this class of cases that rest and posture is most apt to succeed.

For the diagnosis and cure of abscess due to foreign body inhalation, bronchoscopy is the method of treatment, and for the diagnosis of new growth in the lung simulating a true abscess it is invaluable. It is also of value in accurately localizing the lesion in cases which come to radical surgical operation. We advise this method, therefore, in acute abscesses which do not promptly drain with posture, when the location is not near the periphery, in chronic cases for the amelioration of distressing cough and expectoration and for the diagnosis and localization of the lesion.

Under this plan, 7 of the 40 cases reported in this series have been bronchoscoped. One of these cases was cured, 2 were markedly improved, and 4 were not improved and later came to radical operation.

Artificial Pneumothorax. The success of collapse therapy in certain cases of pulmonary tuberculosis very naturally has led to its consideration as a possible useful procedure in other pulmonary conditions and among them lung abscess.

We have employed this method in some cases, but tentatively, in order to have actual experience as a basis of judgment, rather than with great confidence in it as a rational procedure. The reason

for this somewhat experimental method of approach is found in our conception of the radically different objects to be attained in pulmonary tuberculosis as opposed to abscess of the lung. In tuberculosis, rest and immobilization of the lung appears to us to be the prime consideration and for this often partial pneumothorax without any actual compression of the lung is adequate.

In abscess, drainage is the desired object, and by artificial pneumothorax this can only be facilitated by pressure properly applied upon the right point and in the right direction. We do not feel that this can be accurately gauged in artificial pneumothorax. Moreover, it sometimes happens that the air introduced works around into the pleural space near the mediastinum and may actually cut off drainage already partially established, resulting in an exacerbation rather than a relief of symptoms. This has been our experience in some cases and has been reported also by others. We also feel that the expulsive action of the cough, which is, after all, the one most important factor in lung drainage, may be hampered in a lung partially immobilized by a pneumothorax.

Our most serious objection, however, is the very real danger that the pleura may be ruptured when this method is employed in abscesses, with a resulting acute septic empyema necessitating immediate operation and under circumstances which render the danger to life exceedingly great. We have had a few such experiences and reports of similar cases occur rather frequently in the literature.

Tewkesbury[11] is perhaps the warmest advocate of artificial pneumothorax in the treatment of lung abscess and he reports very considerable success. He advocates its use, as soon as the diagnosis is established, the earlier the better, if possible before any pleural adhesions are formed. He does not, however, state that it is not to be used in more chronic cases. Others have also reported successful results but usually in very small series of cases and among these are also some of the unfortunate ruptured cases above noted, and we cannot escape the impression that many cases have been treated without careful study of the other possible methods of treatment and without due regard to the dangers that may be involved.

Upon the whole, therefore, we believe that this procedure carries with it too great a risk to warrant its employment as a routine procedure in the treatment of lung abscess, at the same time realizing that with a fortunate combination of circumstances, especially in lesions situated near the hilum, brilliant results, as in one of our own cases, may be obtained by its use.

In this series, we employed artificial pneumothorax in combination with rest and posture in 10 cases. Of these 1 very promptly recovered and 2 were improved. The remaining 7 were not improved, of these 2 were also bronchoscoped without result and all were later operated on.

Surgical Operation. The treatment of lung abscess has often been considered mainly a surgical responsibility. We have outlined above our plan of management which has for its main object the cure of the condition without recourse to this radical procedure, which is attended by considerable risk and which, even when successful, always results in long weeks or months of purulent discharge with frequent dressings and considerable discomfort, and which sometimes ends in a bronchial fistula, difficult or even impossible to heal. It is obvious that a cure obtained without operation is a much more simple and satisfactory procedure and that this is possible to obtain in a considerable percentage of cases has been demonstrated. Nevertheless, it is our experience that with all our increased effort to obtain a cure without operation, it still eventually becomes a necessary resort in from 40 to 50 per cent of our cases.

The surgical treatment consists in incision and drainage, with the resection of two or more ribs, in one stage if the pleural cavity is walled off by adhesions, otherwise, in two stages. Local anesthesia is safer than general anesthesia even with nitrous-oxide gas and oxygen. A soft rubber dam is the best form of drain, and we have abandoned the use of gauze, employing it only to control hemorrhage.

We found this operation extremely dangerous and usually unsuccessful in the acuter phases of the disease; that is, during that period when there was present about the softened central suppurating focus a more or less extensive zone of edematous, soggy, infected lung in which the smaller bronchi were filled with pus and the alveoli were distended with seropurulent exudate, while the walls of the alveoli were swollen and edematous. None of these cases was seen prior to rupture and establishment of communication with a bronchus.

Our experience has led us to believe that incision of the abscess at this time fails to drain effectively the entire infected area, and that, with a free opening established, the effectiveness of coughing in emptying these areas is greatly reduced. In many of our cases in which the abscesses were opened during this stage, there was a pronounced improvement for a few days, the expectoration was diminished; the temperature became normal, and the patient apparently was making a satisfactory recovery. But this period was followed by a wide extension of the pneumonic process, sometimes ushered in by a chill and a fatal termination in from three to five days or a week. At necropsy, there was found a widespread massive involvement of the entire lung or both lungs, in which the bronchi were filled with pus and the alveoli either showed the changes of an acute pneumonia or were swollen, edematous and infiltrated with leukocytes. In some cases, there were multiple small abscesses widely disseminated throughout the lungs.

After postural drainage, even if it does not effect a cure in itself, there is usually a definite improvement in the constitutional symptoms and a clearing of this secondary zone of infiltration about the abscess, which renders an operation much more liable to succeed.

There is a period in lung suppuration when the alveoli in the immediate vicinity of the abscess are collapsed but the respiratory epithelium is still intact, and they are therefore capable of reaëration and this is the most favorable time to operate. If the suppuration continues, this epithelium disappears and the alveoli are obliterated; and there is found a true connective-tissue layer composed of the fused alveolar walls, observed in chronic abscesses; a condition most unfavorable for a complete cure and one which favors the establishment of a permanent bronchial fistula.

The problem is to give each patient an opportunity to reach this more favorable stage and at the same time not allow the disease either to go on indefinitely or to drift into the chronic abscess with thick fibrous walls, which is unfavorable for radical cure by operation or any other method of treatment. The decision as to when this optimum time for operation has arrived is in our opinion the most difficult and important factor in successful treatment. Our increasing success in three successive series of cases studied carefully during the development of our present methods is mainly due to better judgment in making decisions upon this vital point. We find the comparative Roentgen-ray pictures the best guide. Acute cases show diffuse densities shading off gradually into the surrounding normal lung without any sharp line of demarcation. This we believe represents the zone of pneumonic infiltration above described.

Under rest, posture and bronchoscopy it is almost always possible to obtain a change in the Roentgen-ray picture represented by a diminution in the area of the collateral zone of inflammation and a sharper line of demarcation between it and the surrounding normal lung. When this change is obtained and further clearing tending toward cure does not occur after three or four weeks of observation, we believe that the time has arrived for operation. The most important point is not to operate during the acute inflammatory stage. Upon the other hand, if operation is too long delayed the chronic stage is reached with the increased difficulty of ultimate cure by operation.

Proceeding under this plan, 20 cases of this series, or 50 per cent, came to operation. Of these, 9 were cured, 7 markedly improved, and 4 died. A bronchial fistula resulted in 3 of the improved cases. In the 20 operative cases the preceding treatment had been rest and posture in 11 cases, rest and posture combined with bronchoscopy in 2 cases, artificial pneumothorax had been unsuccessfully employed in 5 cases, and in the remaining 2 cases rest, posture, bronchoscopy and artificial pneumothorax had all been tried without success.

Causes of Operative Deaths. Four of the 20 patients operated upon died, an operative mortality of 20 per cent. These 4 operative deaths comprise all the deaths experienced in our entire series. By our plan of management it is evident that the mortality would be mainly, if not exclusively, included in the operative group, for the reason that cases which do not respond to the other methods of treatment are the ones considered suitable for operation. This brings all of the more serious and difficult cases into the series operated upon, which naturally increases the hazards of that group.

We feel that although our operative mortality has been materially diminished as compared with our previous experiences, nevertheless there is still definite room for further improvement and our especial study at present is directed toward that end.

An analysis of the causes of death in the 4 fatal cases is consequently considered of importance.

Our first operative death was in a case in which no pleural adhesions were found, although expected. Too wide an exposure was made, pneumothorax resulted, the abscess was not reached and death occurred in three weeks. We consider this death due to faulty technique.

The second death was due to a general streptococcus septicemia following operation. This is an unusual complication which, however, will undoubtedly occasionally occur, and we do not see how it could be guarded against.

The third case illustrates the dangers of artificial pneumothorax in these cases. After five such treatments the patient suddenly developed an acute pyopneumothorax due to rupture of pleuritic adhesions. This necessitated an immediate emergency operation which discovered a very foul infection of the pleural cavity with anaërobic organisms and the patient died, as they are very apt to do in such cases. The responsibility of this death should be laid against pneumothorax treatment rather than the resulting surgical operation.

The fourth and last case was a heart-breaking one to lose. A case with very large abscess had been carefully treated by rest and posture and had reached a stationary stage with marked general improvement but no change in the Roentgen-ray picture after several weeks. The collateral zone of inflammation had subsided and the line of demarcation from the surrounding lung had become sharp. We considered it an ideal case for successful operation. The patient did splendidly and was apparently upon a sure road to recovery when twenty days after the operation he suddenly died from a cerebral embolism. This accident is one of the real but fortunately comparatively rare hazards of operation in lung abscess. We do not know how it can be prevented.

In summarizing our experiences with these 4 fatal cases we conclude that in 2, death might have been avoided but not in the

other 2. We believe that an operative mortality of 10 per cent is probably the best that can reasonably be expected in any large series of lung abscesses and that it should be our aim to attain this result.

TABLE I.—RESULTS OF OPERATION.

Series.	Number of cases.	Number operated upon.	Per cent cases operated upon.	Cured.	Improved.	Died.	Operative mortality, per cent.
First . .	29	14	48.3	4	0	10	71.5
Second . .	31	13	41.9	7	1	5	38.5
Third . .	40	20	50.0	9	7	4	20.0
Total .	100	47	47.0	20	8	19	40.0

In the accompanying Table I, the results of operation which we have obtained in three series, two of which have already been reported, are presented. The progressive improvement in the three series is striking and we ascribe it mainly to a wiser selection of the time and stage of the disease suitable for operation.

General Analysis of Clinical Material. Certain general considerations are here presented in order to record the type of clinical material with which we have been dealing in this series of cases.

Etiology. Fourteen cases gave no history of any previous condition which could be considered as a factor in the causation of the pulmonary abscess. These cases we have classified as idiopathic abscesses and the percentage of them corresponds very closely to the number noted in our previous series.

Thirteen cases definitely followed an acute pneumonia.

Five cases were due to a tonsillectomy and 5 were secondary to some other surgical operation.

One followed tooth extraction, 1 seemed directly attributable to prolonged submersion in contaminated water, and 1 followed severe trauma to the chest.

No cases in this series were due to the inhalation of a foreign body.

Duration before Treatment. It is generally recognized that any method of treatment is more successful the earlier it is instituted. Chronic cases are difficult to cure. The length of time that the abscesses have existed therefore would have a definite influence upon the results to be expected.

Of these 40 cases the abscess had existed less than one month in 15 cases, from one to three months in 10, from three to six months in 6 and more than six months in the remaining 9 cases. These last may be considered as chronic cases which thus constituted 22½ per cent of the series.

Location of the Lesion. In 29 cases the lesion was situated in the right lung. Of these, 15 were in the upper lobe, 11 in the lower lobe and 3 in the middle lobe.

In 11 cases the left lung was involved, in the upper lobe in 4 cases and in the lower in 7.

Sex. In our experience, lung abscess is much more common in men than in women. In this series, 31 cases were in men and only 9 in women. This is in accord with our previous experience and with that of other observers.

TABLE II.—SUMMARIZED RESULTS OF TREATMENT.

Series.	Number of cases.	Cured.	Improved.	Not improved.	Died.	Per cent mortality.	Per cent cured or improved.
First . .	29	11	2	4	12	41.4	45.0
Second .	31	14	5	4	8	26.0	61.0
Third .	40	19	17	0	4	10.0	90.0
Total .	100	44	24	8	24	24.0	68.0

Summarized Results of Treatment. The results which we have obtained by the various methods employed have already been indicated. In Table II, the general results obtained are tabulated in comparison with those previously reported in our other two series.

The progressive improvement already noted in the summary of our operated cases is reflected in this table also. This is particularly noticeable in the diminution of the mortality which is only 10 per cent in this last series. In considering the number of cured and improved cases it is to be noted that the percentage of absolute cures reported is only slightly larger in our last series, but many of the cases classified as improved are still under treatment and will, we believe, eventually become cured. This applies especially to the operative group, 7 of which, though doing well, still have discharging wounds and in consequence cannot be included among the cured cases.

Summary and Conclusions. 1. The successful treatment of cases of abscess of the lung is materially aided by their joint management by internist and surgeon, with the close coöperation of a skilled bronchoscopist.

2. A systematic plan of prolonged rest, combined with postural drainage, is the basic method of treatment. Into this plan the other methods may be advantageously introduced in properly selected cases.

3. Bronchoscopy is of real value as an aid to drainage in certain cases. Artificial pneumothorax has a very limited field of usefulness.

4. Approximately from 40 to 50 per cent of all cases will eventually need radical surgical treatment. Correct judgment of the indications for operation is the crucial element in successful treatment. In general, it is based upon the avoidance of surgical intervention during the acute phases of the disease but without delaying too long and thus allowing the case to drift into the chronic stage.

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BACTERIAL VACCINES IN ASTHMA.[1]

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There is so much controversy regarding the use of bacterial vaccines in asthma and I have had so many inquiries from physicians on the subject that I decided to prepare this paper telling in detail a method of diagnosing and treating bacterial asthma that has proven very satisfactory in my hands.

Diagnosis. I will only refer to such points as have a bearing on the diagnosis of bacterial asthma.

History. An exhaustive history should be taken on every asthma case, as invaluable information can frequently be obtained in this way. The age of onset is important, as asthma that starts after the age of forty years is almost always nonsensitive or bacterial in type. This is just what we would expect, as it does not seem probable that a person after forty years would become sensitive to some food or air-borne substance to which he had been exposed all his life. On the other hand, bacterial infection of the respiratory tract would be more likely to occur in the later years of life due to the lowered resistance at this time. Walker stated that none of his patients who developed asthma after the age of forty years were protein-sensitive. There are exceptions to this rule, however, as I have seen a few patients who developed asthma after the age of forty that was definitely proven to be due to sensitization to food or air-borne substances.

Bacterial asthma may be perennial or seasonal in type. The seasonal type of bacterial asthma is frequently limited to the winter months, also commonly occurs during the changeable weather of early spring and late fall. One differential point between the spring and fall seasonal bacterial cases and pollen asthma is that the bacterial cases are more irregular in their time of starting and stopping than the pollen sensitive cases. When itching of the eyes is met with, the case is not likely to be a bacterial one, as definite itching of the eyes is very suggestive of sensitization, in fact is almost always present where sensitization exists to some air-borne substance. The nasal secretion in bacterial cases is likely to be thick, sticky, and frequently yellowish, in contrast to the thin, clear, watery secretion of the sensitive cases, although there may be a thin, watery secretion with a streptococcus infection. Likewise, the sputum in the bacterial case is more likely to be of a greenish-yellow, purulent nature than the grayish-white, jellylike sputum of the sensitive asthmatic. The bacterial asthmatic usually

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has a great deal more cough and expectoration than the sensitive individual. In the bacterial type, as a general rule, cough initiates the attack, whereas in the sensitive type, shortness of breath and wheezing are the first symptoms noted and cough does not usually occur until the attack is breaking up. Between attacks, the bacterial asthmatic frequently has more or less cough and expectoration, whereas the sensitive asthmatic is usually free of these symptoms. In bacterial asthma the most common time for the attacks to begin is in the early morning hours, whereas in sensitive asthma the attacks come on at any time, out of a clear sky, dependent, of course, upon ingestion of, or exposure to, some offending substance. Sensitive asthmatic attacks are usually more abrupt in their onset than the bacterial type. Bacterial cases are usually more susceptible to sudden changes in the weather than sensitive asthmatics. Bacterial asthmatics are also more subject to "colds," sinus trouble, and the like, than the sensitive patients. Bacterial cases will commonly give the history that they never have asthma except when they take "cold." The sensitive asthmatic also occasionally gives this history, when in reality the attacks are not due to taking "cold" at all, as the symptoms simulating a "cold" such as sneezing, running of the nose, watering of the eyes, are merely reactions of the mucous membranes to some offending substance. These sensitive cases may usually be differentiated from the bacterial ones, however, by the fact that in the former the apparent "cold" and asthma may all develop within a few hours, whereas in the latter it usually requires several days for a head "cold" to get down in the bronchial tubes and produce asthma.

Physical Examination. An examination of the nose and throat and the heart and lungs should be included in the study of every asthmatic, especially where the cause is unknown, and all suspicious cases should be referred to specialists for this purpose. A red, inflamed, congested nasal mucous membrane, nasal polypi, inflammation about the orifices of the nasal sinuses, pus exuding from these orifices or lying free in the nasal cavity, pharyngeal inflammation, injection of the tonsillar pillars or definitely diseased tonsils, all point toward bacteria as the cause of the asthma, although of course bacterial infection may be superimposed on a true sensitive asthma. In the true sensitive asthmatic when there are nasal symptoms such as sneezing and rhinorrhea, the nasal mucous membrane appears bluish-gray, boggy or even water-logged, quite a different picture from the membrane of bacterial infection.

Skin Tests. What tests to make and what tests not to make is an important question to be decided in each individual case. I am absolutely opposed to the principle of testing everybody with everything. Every substance should be tested to which the slightest suspicion can be obtained in the course of an exhaustive history. In those patients whose asthma began before the age of

forty years, skin tests should also be made with all food proteins, animal epidermals, pollens, orris root, house dust and miscellaneous substances that the individual patient eats or comes in contact with at least once a week during the season of the year in which he has asthma, or throughout the year if the disease is of the perennial type. If positive reactions are not obtained that are sufficient to account for all of the patient's asthma, tests should also be made with stock bacterial proteins. In those patients whose asthma began after the age of forty, other than making those tests indicated by the history, and tests with stock bacterial proteins, it is sufficient to test the foods and other substances which the patient eats or to which he is exposed every day during the period of the year in which he has asthma.

In testing with stock bacterial proteins I routinely use the following: Staphylococcus pyogenes aureus, Staphylococcus pyogenes albus, Staphylococcus pyogenes citreus, Micrococcus catarrhalis, Micrococcus tetragenus, Streptococcus hemolyticus, Streptococcus nonhemolyticus, Streptococcus viridans, Pneumococcus Type I, Pneumococcus Type II, Pneumococcus Type III, Friedländer bacillus, Diphtheroid bacillus, Bacillus coli communis.

I also make a von Pirquet test at the same time. That portion of the arm where the tuberculin and the glycerine-bouillon control are to be applied is first wiped off with ether. When a definitely positive reaction is obtained to a von Pirquet test, especially if it occurs immediately, the sputum should be carefully searched for the presence of bacillus tuberculosis and an examination of the lungs should be made by some competent chest man, which examination should include Roentgen-ray study.

Skin tests with bacterial proteins are left on about thirty minutes and then washed off with sterile water and if any of them appear suspicious in comparison with normal controls, notation is made to that effect. The patient is then requested to return the next day for inspection, to see if there are any delayed reactions, being instructed not to irritate the tests any more than is necessary in the meantime. These delayed reactions appear about the site of the scratch tests and are red, inflamed, swollen, hot, tender or even painful, having all the appearances of a mild infection. Occasionally a sterile pustule forms at the site of the scratch. A reaction $\frac{1}{2}$ inch in diameter I call a + 1 (+), a reaction 1 inch in diameter a + 2 (++), etc.

In my experience I do not remember a single case where tests with stock bacterial proteins gave a definitely positive immediate reaction, manifested by an urticarial wheal with pseudopods, such as described by Walker and others. Delayed reactions to stock bacterial proteins on the other hand do occur, and although relatively infrequent, they are of considerable diagnostic importance, which to my mind justifies testing with the bacterial proteins.

Staphylococcus pyogenes aureus, Streptococcus hemolyticus and Staphylococcus albus have been the most frequent reactors in my hands.

Blood Tests. Blood tests are of considerable help in the diagnosis of asthma. Where the leukocyte count is above 10,000 and the polymorphonuclears are around 80 per cent or more, a diligent search for some focal infection is indicated. Where there is a relative increase of lymphocytes at the expense of the polymorphonuclears, it is suggestive of three things: (1) Tuberculosis; (2) lues, and (3) latent streptococcus infection, which should of course be ruled out in the individual case. A Wassermann test should be made on all patients who give a suspicious history, such as repeated miscarriages, and so forth. A Wassermann test should also be made in all cases of continuous asthma, as lues is something we have to think of in all chronic, undiagnosed conditions. For example, I have had two patients with continuous asthma who gave positive Wassermann reactions and were almost immediately relieved of their asthma on antiluetic treatment. Both of these patients had an aortic aneurysm.

Some writers have maintained that eosinophilia in an asthmatic is practically diagnostic of protein sensitization. I am forced to disagree with them on this point, however, as I have seen definitely protein-sensitive asthmatics who had no eosinophilia whatsoever, either during or between attacks. Furthermore, some of the highest eosinophile percentages with which I have met, have been in nonsensitive or bacterial cases.

In an asthma case, where a complete history and physical examination, blood tests, Roentgen-ray study, and skin tests with foods, animal epidermals, pollens, stock bacterial proteins, orris root, house dust and other miscellaneous substances, fail to reveal any cause for the dyspnea, I assume that I have made a diagnosis by elimination, of bacteria as the cause of the asthma.

Cultures and Vaccines. The patient is given a sterile sputum bottle wrapped in a clean paper towel and told not to open it until ready for use. He is instructed to wait until he has asthma and as the attack is breaking up and he brings up some of the thick mucus that seems to come from down in his lungs, not saliva out of the mouth nor secretion that drains down from the nose, but what is actually coughed up, he is to open the bottle and spit into it, being very careful not to touch the inside of the bottle or the bottom of the stopper with the fingers; then cork it up tightly and take or send it to my bacteriologist as soon as possible. He is told that if he collects it during the night he is to see the bacteriologist the next day, and if in the morning, he is to see him the same day. At this time cultures are also taken from the nasal secretion (anterior and posterior) and from the throat. Immediate smears are examined and plates and subcultures are made on placenta infusion blood

agar, human blood agar, and such other media as may be indicated. From these the various organisms found are isolated in pure culture, and a vaccine is prepared from each containing two billion organisms per cubic centimeter. The vaccines are killed by heat and held several days for sterility tests. They contain no preservative whatsoever, as we feel their use to be unnecessary where the vaccines are to be handled with strict aseptic precautions. Also, preservatives cause reactions at times that are misleading to the physician and may be decidedly unpleasant for the patient. The vaccines are, of course, kept refrigerated. No vaccine is kept more than one year from date of preparation. All our vaccines are put up in 20 cc. rubber-capped glass vials with a removable glass cap containing a pledget of cotton soaked in 5 per cent phenol. A few sterile glass beads are placed in the vaccine container to facilitate shaking.

Intradermal Tests. The patient is tested intradermally with each of his vaccines, using sterile physiological saline, containing a trace of agar, as a control. We include a trace of agar in our control as we felt that our vaccines probably contained a trace from the culture media, and agar might be irritating to some skins, thus giving us a false reaction. Sterile tuberculin syringes and fine needles (26 gauge, $\frac{1}{2}$ inch) are used for making the tests. The needles should be sharp and free from rust or corrosion, as otherwise we unduly traumatize the skin and may leave a dark spot in the skin. Most writers in giving the technic of intradermal testing say to inject some measured quantity of fluid, namely, 0.01 cc., 0.02 cc., 0.05 cc., or 0.1 cc. My experience with tuberculin syringes is that they all leak more or less, after they have been used a while, so even though you start with some definite amount, there is no telling how much enters the skin, as a considerable portion may "backfire" alongside the piston. When fluid is injected intradermally a wheal or blister is formed immediately, and equal quantities of fluid will produce approximately the same sized wheals. In testing bacterial vaccines intradermally, I start with any where from 0.1 cc. to 0.25 cc., depending upon the apparent tightness of my syringe, and inject sufficient to produce a blister approximately $\frac{1}{4}$ inch in diameter. By this method I feel that I have injected an approximately equal quantity of each of the vaccines and the control, and therefore can fairly compare the subsequent reactions. In making intradermal tests with food, animal epidermal, pollen and other extracts, it is only necessary to inject enough fluid to produce a minute wheal, say $\frac{1}{8}$ inch in diameter, but in testing bacterial vaccines where the quantity of allergic material is probably small it seems desirable to me to inject the larger quantities. I have been able to obtain but little diagnostic information from inspection of intradermal bacterial vaccine tests after thirty minutes,

as considerable traumatic inflammation is usually present and furthermore it has not been my experience to see definite urticarial wheals with pseudopods appear. However, if any of the tests have a larger wheal or show more inflammation than the control, notation is made to that effect. The patient is requested to return the next day for inspection of the tests, being instructed not to irritate them any more than is necessary in the meantime. Delayed reactions to intradermal vaccine tests differ only in degree from those obtained with stock bacterial proteins, being much more marked as a rule, and they are charted in the same way, that is, a reaction ½ inch in diameter is called a + 1 (+), and so forth. When the control is also inflamed the diameter of this inflammation must be subtracted from that of the vaccine tests in order to estimate the true size of the bacterial reactions. Positive reactions to intradermal autogenous vaccine tests are just as common as positive reactions to cutaneous tests with stock bacterial proteins are rare. Those vaccines which fail to show a reaction in twenty-four hours are discarded and those which react are used for treatment.

TABLE SHOWING RESULTS OF INTRADERMAL VACCINE TESTS.

Organism.	Number of tests.	Number of positive reactions.	Per cent of positive reactions.
Staphylococcus pyogenes aureus	87	71	82
Streptococcus hemolyticus	79	23	29
Streptococcus viridans (nonhemolyticus)	67	16	24
Staphylococcus pyogenes albus	12	9	75
Pneumococcus	12	3	25
Micrococcus catarrhalis	10	8	80
Bacillus mucosus capsulatus (Friedländer)	9	9	100
Diphtheroid bacillus	7	6	86
Bacillus coli anaërogenes	1	1	100
Bacillus pyocyaneus	1	0	0
Totals	285	146	51

Treatment. If the test reaction was marked the initial dose is 0.025 cc., or 50,000,000 organisms; if the reaction was moderate the first dose is 0.05 cc., or 100,000,000; and if the reaction was very slight or doubtful the first treatment is 0.1 cc., or 200,000,000. If there are two or more vaccines to be given in any one case and the test reactions were nearly equal, an equal dose of each one is drawn into the same syringe and all injected together, the dose of each one being the same as if that were the only one being given. If one vaccine gives a marked test reaction and another vaccine gives a relatively mild reaction, a small dose of the marked reactor is injected in one arm and a larger dose of the mild reactor is given in the other arm. The patient is instructed to look at his arm or

arms the next day, about twenty-four hours after treatment, to see if there is any local reaction, namely, if there is a red spot or not, and, if so, about how large. A red spot twenty-four hours after treatment the size of a dime or larger is called a local reaction. Treatments are given regularly every five to seven days, preferably the latter. The second treatment is usually double the dose of the first, and for each subsequent treatment the dose is increased by the amount of the first treatment, providing a local reaction is obtained each time. It is desirable to obtain a local reaction from every treatment, so if any individual injection fails to give such local reaction, the dose for the next treatment is increased by the amount of the first treatment plus the amount of the previous increase. For example, if the first treatment is 50,000,000, the second would be 100,000,000, the third 150,000,000 and so on, provided a local reaction occurs each time. If the first treatment is 50,000,000 and reacts, and the second treatment of 100,000,000 should not react, the third injection would be 200,000,000 and if this treatment reacted, the fourth would be 300,000,000 and so on. If a marked local reaction, that is, an extremely sore arm, or a constitutional reaction such as a definite aggravation of the asthma should follow any individual treatment, the same dose should be repeated for the next treatment, or it may even be advisable to go back to the previous dose which failed to produce such reaction. Treatments are continued until a maximum dose is reached or until the vaccine is used up. It is my rule never to inject more than 2 cc. of vaccine (4,000,000,000 organisms) in any one arm at one time.

If for one reason or another a patient's treatments are interrupted it becomes necessary to decide what dose to give when he returns. If approximately two weeks have elapsed since the last treatment I repeat the same dose. If approximately three weeks have elapsed, I go back to the dose of the next to the last treatment, and so on. In other words, I take the number of weeks that have elapsed since the last treatment and subtract one, which gives me the number of treatments to count back to arrive at the proper dose. If a patient has been doing nicely on vaccine treatment and later fails to respond to the same treatment, fresh cultures should be taken and vaccines prepared and tested as before, as the patient's flora have probably changed. In certain acute cases of asthmatic bronchitis it seems unwise to wait for the preparation of autogenous vaccines, and a stock, mixed respiratory bacterin is used instead.

Results. One hundred and forty-four cases of asthma have been treated with bacterial vaccines according to the method described in this paper. Of these, 74 cases or 51 per cent were completely relieved of asthma, 56 cases or 39 per cent were improved in varying degrees, and 14 cases or 10 per cent were unimproved. In other words, 90 per cent were completely or partially relieved of their

asthma and in only 10 per cent of the cases was the treatment a failure.

Discussion. The method of diagnosing and treating bacterial asthma as given in the preceding part of this paper has been arrived at by a process of evolution. When I first started to treat asthma, autogenous vaccines were used in all cases which failed to react to skin tests with the proteins of foods, animal epidermals, pollens, and the like. These vaccines were prepared from cultures obtained from the sputum, and in an occasional case where there were definite nasal symptoms, cultures were also taken from the nasal secretion. Whether a dominant organism or a mixture of several organisms was to be used, was left to the judgment of the bacteriologist. Only one type of vaccine was prepared for each case, but in two separate concentrations: 1,000,000,000 organisms per cubic centimeter and 5,000,000,000 per cubic centimeter. Treatment was started with 0.1 cc. of the weaker vaccine, which dose was increased by about 0.1 cc. each time until a dose of 1 cc. was reached, then changed over to the stronger vaccine, starting with about 0.2 cc. and increasing in a similar manner as before until a maximum dose of 5,000,000,000 had been reached. I noted that a number of patients who were entirely free of asthma on the smaller doses, would unexpectedly blow up with asthma on the larger doses of the stronger vaccine, so we compromised on a single concentration of 2,000,000,000 organisms per cubic centimeter. My vaccines were formerly put up in 1-cc. glass ampules, which, although it ensured that the vaccine would remain sterile until used, was very wasteful of vaccine on the smaller doses, and considerably more troublesome to handle than the single, rubber-capped, glass vial. Treatments were originally given twice a week but it seemed that patients did better as a general rule with a weekly interval, especially on the larger doses.

It was observed that in patients who got local reactions from treatments the results were usually good, whereas in patients who got no local reactions the treatments were almost invariably a failure. Cutaneous or scratch tests were found to be of no avail for testing vaccines, undoubtedly due to the fact that the reacting substance is bound up in the bodies of the bacteria. In view of this it was decided to perform an intradermal test with the autogenous vaccine prepared in each case before treatment was started, and if no reaction was obtained from the test, it was thought best to discard the vaccine and obtain new cultures. Where a positive reaction was obtained by the intradermal method to a vaccine containing two or more different types of germs, it was impossible to tell which one was the offending organism. We therefore prepared a dry, powdered protein from every one of the various types of organisms isolated in the individual case, and the patient was

tested cutaneously with the same. These proteins were extracted with alcohol and ether, after the method described by Walker. The principal obstacle met with was in getting the proteins dry, and as a separate set of proteins had to be prepared for each case, it was quite a job. As the proteins had to be dissolved again in making the tests, it was finally decided not to attempt to dry them at all, so the individual protein extracts were put up in capillary glass tubes with the ends sealed, and labeled, until such time as the tests were to be made. The dry, powdered proteins and the liquid protein extracts were prepared and tested on a very large number of patients, but in only a single instance was a definite positive reaction obtained and that was to the protein of Staphylococcus aureus. In most of these same patients however a vaccine prepared from the same organism as the proteins would give a positive intradermal reaction. It was inferred from this that our laboratory methods of extracting the allergic substance from bacteria were sadly deficient, and as we could get the patient's own tissue cells to do this for us by means of the intradermal vaccine test, why bother with it at all? Therefore, we adopted the method of preparing a separate vaccine from every organism isolated in the individual case, and testing the patient intradermally with the same, interpreting the reactions after twenty-four hours.

Rackemann states that he has found the intradermal method of testing vaccines unsatisfactory for the reason that certain organisms give large local reactions on each and every individual. This has not been my experience in testing the respiratory infection organisms, with the exception of Friedländer bacillus (see table).

Rackemann tests the vaccines by injecting subcutaneously about 500,000,000 organisms of each, interprets the local reactions twenty-four hours later, and selects the vaccines for treatment that react, and discards those that do not. I am opposed to the injection of such large test doses, because of the probability of aggravating the patient's trouble.

Agglutination tests were also performed on a considerable number of cases, using the patient's own blood serum in varying dilutions: 1 to 12½, 1 to 25, 1 to 50 and 1 to 100, against each of his own organisms and also, in most cases, against Staphylococcus aureus obtained from another asthmatic. More or less agglutination of every organism was obtained with a dilution of 1 to 12½, but with a dilution of 1 to 100 agglutination occurred in only one solitary instance. That was with a Staphylococcus aureus and the patient's own serum, and this was the aureus just referred to that was tested against other patients' blood sera. Because of the extremely discouraging results from agglutination tests we discontinued them.

The bacteriological and serological work has been performed by Dr. O. B. Hunter, professor of bacteriology and pathology,

George Washington University Medical School, and I wish to take this opportunity to express my appreciation of his ever willing and able coöperation.

I am fully conscious of the fact that Cooke, Bernton and others maintain that bacteria are never the fundamental cause of asthma, but are merely secondary invaders; that cutaneous tests with stock polyvalent bacterial proteins are useless and unreliable, as reactions seldom occur and when they do are likely to be to some organism that cannot be isolated from the patient; that the use of vaccines is illogical; that it is never possible to shock a patient to the extent of producing an attack of asthma with a bacterial vaccine, as can be done with other types of protein extracts; and that where good results are obtained by the use of bacterial vaccines it is always due to nonspecific action. I am forced to disagree with all of these opinions. If patients can have asthma from becoming sensitive to the proteins contained in foods, animal epidermals, pollens, and so forth, why cannot they also have asthma from becoming sensitive to the proteins contained in the bodies of bacteria? It is true that reactions to cutaneous tests with stock, polyvalent bacterial proteins are seldom obtained, probably due to imperfect methods of extraction, but when they have occurred in my experience have usually been of valuable diagnostic significance. Very rarely a reaction is obtained to some organism that cannot be isolated from the patient but this is nothing against the value of the tests, as we must remember that the organism may be present in some remote part of the body such as the appendix, gall bladder, or intestinal tract, or the reaction may represent a sensitization produced by some previous infection that has ceased to exist, such as a boil, carbuncle or infected tonsils. I have produced an attack of asthma out of a clear sky innumerable times by too large a dose of vaccine. The attack of asthma occurs coincident with the reaction on the arm. If the good results from the use of bacterial vaccines are always due to nonspecific action it would seem that large doses would work better than small ones, but I have repeatedly found the reverse to be the case.

Summary. A detailed description is given of a method of diagnosing and treating bacterial asthma.

One hundred and forty-four cases of asthma have been treated with bacterial vaccines in accordance with the method described, and of these cases, 51 per cent were completely relieved of asthma, 39 per cent were improved in varying degrees, and 10 per cent were unimproved.

The various steps taken by the author in arriving at the present method are briefly outlined.

Certain objections to the use of bacterial vaccines in asthma are referred to and answered.

THE MECHANISM OF THE FLOW OF BILE FROM THE LIVER INTO THE INTESTINES.

Conclusions from Previous Studies.

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and

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The physiology of the gall bladder and biliary passages constitutes a complex problem. In several papers[1, 2, 3, 4] we dealt with various phases of the subject from an experimental point of view. It is our present purpose to integrate the results of these studies and to apply them to a theoretical conception of the mechanisms involved in the flow of bile from the liver into the intestinal tract.

Bile is secreted continuously into the hepatic ducts by the liver. The rate and quantity depend on several factors; for example, much less is secreted during the fasting state. It is generally thought that the liver cells actively secrete bile and the secretory pressure has been estimated as approximately 300 mm. of bile.[5] This is usually measured by placing an upright manometer in the common duct, tying off the latter beyond the cannula and occluding the cystic duct at the same time. It should be pointed out at once, since this has given rise to confusion in the discussions of the problem at hand, that the secretory pressure so measured is the maximum pressure that the liver cells are capable of exerting against an obstruction and not the same as exists in the common duct under normal conditions. Here the liver is secreting into a duct system which includes a distensible gall bladder and a relaxable sphincter of Oddi.

By inserting a *T* cannula in the common duct, instead of blocking it, we found that the pressure in the common duct of the dog during the fasting state and under anesthesia is relatively low. It measured 60 to 70 mm. of bile, with the cystic duct occluded and varied little, only 3 to 6 mm., with respiration. Bürker[6] obtained similar figures for the normal intraductal pressure.

This is considerably less than the resistance which the sphincter of Oddi offers to pressure from the common duct side, which averaged in our series of dogs 120 to 130 mm. of normal saline. Such a tonus figure is probably fairly constant during the fasting state. It is true that we did observe occasionally a spontaneous ooze of a few drops of bile or the escape of a few drops with each inspiration through the sphincter of Oddi into the duodenum during the fasting state. The significance of this, as well as the entire question of the sphincter control, will be discussed later.

We may state, then, that bile is secreted continuously into the hepatic ducts and is present in the common duct under a pressure of 60 to 70 mm. of bile. It meets the closed sphincter of Oddi which presents a resistance of 120 to 130 mm. of saline. Since it cannot distend the rather rigid liver tissue, and since the cystic duct offers only the slight resistance of 30 mm., the bile flows through the cystic duct into the gall bladder. Rous and McMaster found that a pressure of 60 mm. of bile was sufficient to fill the dog's gall bladder through the cystic duct.[7]

The question arises at once as to whether the pressure within the gall bladder permits this inflow. This is dependent on the phase of respiration. During expiration the pressure in the gall bladder is the result of the hug of its elastic, muscular wall on its contents. We have noticed that the gall-bladder wall accommodates itself to its contents. This is probably brought about by a reflex act. The actual pressure within the gall bladder depends on the tonus of its musculature and elastica, and this probably on the inherent irritability of these tissues as well as on the innervation tonus. The tension of the wall about its contents is of great importance, as we shall see later, in permitting the increased intra-abdominal pressure, due chiefly to the inspiratory phase of respiration, to effect a large increase in the intravesical pressure. In our studies we found that the pressure resulting from the tension of the wall averaged the low figure of 35 mm. of bile during expiration. It will be seen at once that this is lower than the pressure in the common duct, so that during expiration bile may flow into the gall bladder. During inspiration a different state exists. As a result of the increased intraäbdominal pressure, the pressure within the gall bladder rises to 100 mm. of bile or slightly over. At this phase bile cannot enter the gall bladder, but must remain in the duct system. Bile from the gall bladder, on the other hand, can be expelled into the common duct through the cystic duct. It does not then enter the duodenum necessarily, since the sphincter tonus, 120 to 130 mm. of saline, is still somewhat greater than the pressure within the gall bladder at inspiration.

There is also another factor to consider here. Either because of the individual anatomical relations or because of respiration, it is possible for a kinking of the cystic duct to be present. In such a case, of course, the increased pressure during inspiration may be ineffectual in driving bile out of the gall bladder. This may be true in a certain number of instances, and thus accounts for individual variations in both filling and emptying of the gall bladder. As a matter of fact, we have observed in our experiments on the color of bile that in the fasting animal dark bile may be present in the common duct as well as in the gall bladder. Furthermore, in our studies we noted fluctuations in the common duct pressure, which were transmitted from the respiratory pressure changes within the gall bladder.

To summarize, we may say that in the fasting state, during expiration, bile enters the common duct, meets the closed sphincter of Oddi, backs up through the cystic duct and enters the gall bladder. At inspiration some bile from the gall bladder is driven into the duct system without entering the duodenum, except for the occasional escapes noted above. Due to the rapid concentrating activity of the gall-bladder mucosa,[7] it seems probable that what leaves the gall bladder represents the considerably larger amount of bile which entered it.

We have found that when the sphincter of Oddi is kept patent by means of a small glass cannula, as described in our studies on the entrance of bile in the duodenum,[3] the gall bladder does not fill. It remains completely collapsed, all of the bile flowing immediately into the duodenum. This demonstrates the importance of the sphincter in the filling of the gall bladder. Such a mechanism as we have described, that is, the liver secreting bile into the ducts, a distensible and concentrating gall bladder to take up the secreted bile, and the pressure factors due to the respiratory act plus the resistance of the sphincter of Oddi, seems to offer a plausible and logical explanation of the filling as well as the emptying of the gall bladder.

It remains now to consider the entrance of bile from the liver and the gall bladder into the duodenum. We have seen that the bile, as it is secreted by the liver into the ducts, meets the resistance of 120 to 130 mm. of saline offered by the sphincter of Oddi and backs up into the gall bladder. There then follows, with the respiratory act, an ebb and flow between the gall bladder and ducts. But we know that occasionally, even in the fasting state, a little bile enters the duodenum, and that during the feeding state a fairly large quantity enters. In fact, as estimated by pigment studies, biliary, common duct and duodenal fistulæ, it is found that 800 to 1000 cc. of bile are produced by the liver daily, and probably most of this in more or less concentrated form enters the duodenum.

It is apparent that the sphincter of Oddi, like the pylorus, is the "keeper of the gate." The factors controlling its tonus seem to be of prime importance in the mechanism of the entrance of the bile into the intestine. We have already presented experimental studies on its control.[2] It seems that the substances present in gastric chyme, such as dilute hydrochloric acid, peptones, dextrose and fat, when placed on the papilla of Vater relax the tonus of the sphincter of Oddi. Twenty-five per cent of magnesium sulphate acts likewise. Furthermore, pilocarpin given subcutaneously increases its tonus, while adrenalin and atropin decreased it. We found no evidence of reciprocal innervation or contrary action between the gall bladder and the sphincter. In fact, pilocarpin increased the tonus of the sphincter and the gall-bladder wall

simultaneously, while atropin and adrenalin relaxed the tonus of both. It was further found that substances which relax the sphincter of Oddi locally, particularly 25 per cent of magnesium sulphate, did not change the pressure within the gall bladder, although they lowered the tonus of the sphincter. Moreover, increasing the pressure in the gall bladder had no effect on the tonus of the sphincter of Oddi. It seems probable that the stimulation of the vagus nerve excites the gall-bladder musculature as well as the sphincter of Oddi, and the sympathetic nerve inhibits both. We do not know how substances act locally to relax the sphincter, but the fact is beyond doubt.

At this point one observation deserves emphasis. In these experiments the tonus of the spincter was only reduced one-fifth or one-sixth below the original figure. In any case it did not go below 90 mm. of saline. While it is obvious that the sphincter must be opened in order to allow the entrance of bile into the duodenum, yet this is not in the nature of a complete relaxation or loss of tonus. The failure to distinguish between a lessening of the resistance of the sphincter by a moderate decrease in its tonus and a complete loss of tonus with a widely opened sphincter has caused confusion in the discussion of the problem. It has been suggested that with the sphincter open practically no pressure is necessary, and that the bile from the gall bladder and liver merely flow by gravity or slightly aided by muscular and intra-abdominal pressure into the duodenum. It seems probable, however, that like other sphincters in the gastrointestinal tract, the sphincter of Oddi maintains its tonus and that certain nervous and chemical stimuli decrease it somewhat. The tonus is not, however, completely lost under normal conditions. It may seem, moreover, from our studies that a pressure of 90 mm. of saline at least is necessary to overcome the sphincter, even when its tonus is decreased by substances acting either locally or through the vegetative nervous system.

When the sphincter is not relaxed, and presents the usual tonus of 120 to 130 mm., the pressures prevailing normally in the common duct (60 to 70 mm. of bile) and in the gall bladder (35 mm. from the tensity of its wall and 100 mm. or slightly over at the end of inspiration) are insufficient to overcome it. Of course, it is possible, under conditions of greatly increased intraäbdominal pressure (vomiting or coughing), that even the tonus of the unrelaxed sphincter may be overcome and bile thus enter the intestine. To repeat, then, when the sphincter of Oddi is partly relaxed a pressure of 90 mm. or over seems necessary to overcome it. What provides this pressure?

We have already pointed out that the usual pressure in the common duct, as distinguished from the maximum secretory pressure of the liver, is quite low—60 to 70 mm. of bile. If we

assume that this is the usual pressure, then it seems as if during expiration, even when the sphincter of Oddi is relaxed, the bile secreted into the common duct by the liver cannot enter the duodenum. At inspiration, however, the pressure in the gall-bladder rises to 100 mm. or over, and this is sufficient to drive some bile from the gall bladder and common duct into the duodenum.

An objection may be raised at once to the belief that the gall bladder is necessary to drive even the liver bile into the duodenum. It may be asked how the bile gets into the duodenum after cholecystectomy. In answer, it may be stated that several observers (such as, Rost, Judd and Mann,[9, 10]) have found that after excision of the gall bladder the ducts dilate widely if the sphincter retains its tonus and thus act as a gall bladder, or the sphincter loses its tonus almost completely, very little pressure sufficing to overcome it. We have also observed in some studies on the sphincter tonus in the same animal, before and after cholecystectomy, that the ducts may dilate and the sphincter lose its tonus as well. Mann[11] found that the sphincter tonus was only 30 mm. in species without a gall bladder.

The above description of the manner of the entrance of the bile into the duodenum may be summarized by stating that under the local relaxing effect of the gastric chyme, and probably also reflexly through the vegetative nervous system, the tonus of the sphincter of Oddi is reduced sufficiently so that the rise in pressure in the gall bladder and common duct during inspiration opens the sphincter, and bile from the gall bladder and liver flows into the duodenum.

Our experimental studies give much support to this description of the mechanics of the biliary outflow system.

Although many forms of local, general and reflex stimuli were separately applied to the anesthetized operated animal, a gross contractile emptying of the gall bladder was never observed. In the roentgenographic studies of Winkelstein[12] and Abramson[13] contractile motions of the gall-bladder outline were not seen. It seems probable that the function of the elastic wall of the gall bladder is to accommodate that organ to its changing content. This maintains a moderate degree of intravesical pressure which possibly renders the inspiratory squeeze more effectual.

We had experimental evidence that a definite dyed specimen of bile may entirely leave the gall bladder of a healthy animal in twenty-four to fifty hours. Since contractile emptying had not been observed, and since bile did leave the gall bladder to enter the duodenum, another explanation had to be sought. On several occasions during the fasting state bile was observed to enter the duodenum at each inspiration. Also in the experiments in which the sphincter of Oddi was kept patent, dyed bile from the gall bladder entered the duodenum with each inspiration. In the fluoroscopic studies already mentioned compression of the gall bladder

in a craniocaudal direction could be seen at each inspiration. Furthermore, the studies on the pressure variations in different parts of the biliary tract demonstrated the comparatively great fluctuations in intravesical pressure produced by the respiratory act. Apparently the relations are so nicely adjusted that when the sphincter is unrelaxed bile flows into the gall bladder because the inspiratory act is not sufficient to overcome the sphincter's resistance, but when the sphincter is properly relaxed the pressure in the gall bladder due to inspiration is adequate to drive bile into the duodenum.

Most experimenters in this field have assumed that increased abdominal pressure operates equally throughout the abdomen and is, therefore, not of importance. They have not realized, as our pressure studies show clearly, that the same factor acting on different structures produces different pressure changes within them, depending chiefly on their size, shape, outlets, wall and contents. A pressure which produces a large fluctuation in the gall bladder, for example, effects less change in the duodenum and almost none in the common duct. Certainly, mechanical forces as well as neuromuscular arrangement and action play a large role in the physiology of the abdomen.

An interesting illustration of the mechanism which we have described above occurred in one of the experiments performed by McMaster and Rous in their studies on the total bile.[8] After tying off the cystic duct they connected a tube from the common duct to a toy balloon. From the further end of the balloon they led a tube out through the lateral abdominal wall. "Once in every twenty-four hours the outlet tube was opened. The intraäbdominal pressure caused the bile to gush forth rapidly and emptied the thin-walled balloon completely, proven by the failure to obtain more bile by aspiration and by washing the balloon with sterile salt solution." Substitute the gall bladder for the balloon, the ducts for the tubing and relax the sphincter of Oddi instead of opening the outlet tube, and you have an analogous mechanism. The lack of rapid complete emptying in the human gall bladder may be explained by the intermittent opening of the sphincter of Oddi.

Although our theory need not necessarily be correct merely because it explains phenomena, yet, since we have adduced some experimental and theoretical evidence in its favor, it is interesting to apply it. What happens during the fasting state and after meals is perhaps obvious from the preceding exposition. Most interesting is the possible explanation of the Meltzer-Lyon test. In this, after the instillation of a 25 per cent magnesium sulphate into the duodenum, bile-stained fluid is obtained, which is at first light yellow in color and then dark brown and then light yellow again. According to Lyon[14] the dark specimen is from the

gall bladder, and is thought to be discharged into the duodenum by a contraction of the gall bladder following a relaxation of the sphincter of Oddi.

With reference to the active expulsion of the gall-bladder bile, our experimental work indicates that the reciprocal action described by Meltzer[15] does not exist, but rather that the magnesium sulphate relaxes the sphincter of Oddi and that then the intraäbdominal pressure squeezes the bile from the gall bladder and ducts through the sphincter into the duodenum.

One important point in the Meltzer-Lyon method of studying gall bladder disease, namely, that the dark bile comes from the gall bladder and that its absence signifies an occlusion of the cystic duct, we can substantiate experimentally in normal animals. In our studies on the color of the bile,[4] liver bile, liver and gall bladder bile and duodenal bile were studied simultaneously by placing cannulæ separately in a hepatic duct and the common duct and a tube through a stomach fistula into the duodenum. We found in the fasting state the bile from the liver was invariably light yellow. In the common duct (from the gall bladder and liver) it varied from a dark greenish brown to a dark brown or tarry, while the duodenal contents, due chiefly to dilution factors, imperfectly imitated the common duct contents. Later the same animals were cholecystectomized and only light-yellow bile was obtained thereafter. It is apparent, therefore, that the gall bladder is the cause and source of the dark bile. In general, it may be said, although the theoretical basis of the test does not appear sound in the light of our experiments, the Meltzer-Lyon is essentially correct in practice.

Summary. The liver secretes bile continuously into its ducts. The sphincter of Oddi then acts as "keeper of the gate," for when it is unrelaxed it offers a sufficient resistance to shunt the bile into the gall bladder. This is made possible by the fact that the pressure within the gall bladder is lower during expiration than the pressure existing normally in the common duct.

At inspiration, with the sphincter still unrelaxed, the increased intraäbdominal pressure raises the pressure in the gall bladder and some vesical bile (if there is no kinking at the cystic duct) flows into the common duct. There takes place then an ebb and flow of bile between gall bladder and common duct when the sphincter is closed.

When the sphincter of Oddi is somewhat relaxed by the gastric chyme or innervation changes the intraäbdominal pressure at inspiration apparently squeezes bile from the gall bladder into the duodenum.

Neither a reciprocal action between the sphincter of Oddi and gall bladder nor sufficient contractile power of its musculature to empty the gall bladder was found in our experiments.

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STUDIES ON THE BLOOD PRESSURE LOWERING PRINCIPLE IN THE SEED OF THE WATERMELON (CUCURBITA CITRULLUS).

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With the abrupt onset of feverishness, pain over the bladder, frequency of micturition, the first thought to enter the mind of a good country housewife was "bladder trouble," and according to a time-honored custom, she immediately procured some watermelon seed, dried them, crushed them, and made a "tea" to offer the patient, not so much as a beverage, but for what she believed to be a specific remedy for the ailment. After a few doses of this, there was a rapid abatement of the symptoms of acute cystitis. Clinicians of the older school frequently prescribed this infusion and claimed success.

With this historical background, it was decided to make a study to discover, if possible, what active substance, if any, in the seed produced the result.

Analyses failed to reveal any alkaloid as the active principle, and attention was directed to the possible presence of glucosides or saponins.

Five hundred grams of the seed were reduced to about a No. 30 powder. This was then macerated for twelve hours with 1500 mils of distilled water which had been rendered slightly alkaline with ammonium hydroxid and previously heated to 60° C. This brownish-yellow infusion was then strained through cheesecloth or gauze

and was filtered several times until very clear. It was then concentrated over the waterbath to the viscosity of a thin syrup, the water in the outer vessel being allowed to boil during the whole process of evaporation. Powdered lead subacetate was added to the concentrated infusion and with vigorous and constant stirring a copious, curdy, yellowish precipitate formed quickly. This was done to precipitate the organic matter containing the glucoside or saponin. The residue was then filtered and washed several times with distilled water. Hydrogen sulphid was vigorously bubbled through this precipitate until it had been decomposed as much as possible. This step was for the purpose of freeing any of the substance in question that may have been caught in the precipitated organic matter and to remove the lead from the preparation. It was then strained through gauze and filtered. Next the filtrate was concentrated to one-half the volume and filtered again until very clear. A little of the lead sulphid settled out and the preparation was rendered free of lead by filtering while hot. Hydrogen sulphid was again bubbled through for a few minutes to make sure there was no lead left in the infusion. It was found well to filter this again as the preparation was not perfectly clear. Equal parts of ethyl ether and dehydrated ethyl alcohol were mixed and added in excess to the clear solution mentioned above. This resulted in a finely divided, creamy-white precipitate. The precipitated drug was allowed to settle completely after which the clear supernatant fluid was poured off. The precipitate was dried on a waterbath over a low flame, and this dried substance was the material to be tested. A little was dissolved in distilled water and its soapy appearance in this solvent directed our attention to the saponin group at once, and tests were carried out as follows:

Five milligrams of the drug were sprinkled into 5 mils of concentrated sulphuric acid. The result of the oxidation was first a yellowish color, which rapidly changed to a bright red, and this in turn, rapidly gave a light brown color, and then a brownish-black. Many saponins are said to give this reaction with concentrated sulphuric acid.

To each of two dry test tubes was added 5 mils of 0.9 per cent solution of sodium chloride. Then were added to each tube, 10 drops of defibrinated sheep's blood. Five milligrams of the drug were added to Tube A; Tube B was used as a control, and received none of the drug. Both tubes were allowed to stand at room temperature for twenty minutes. At the end of this time, there was a definite change of color in the blood of Tube A, from bright red to a light chocolate-brown, and gradually a brownish sediment settled to the bottom of the tube. A slight degree of hemolysis also occurred. However, the blood in Tube B remained unchanged, thus demonstrating the laking and precipitating action of the drug on the cellular constituents of the blood. This, it will be remem-

bered, is a peculiar property of the saponins and agglutinins which occur in many seeds. After the observation, both tubes were placed in a refrigerator together. Twelve hours later, the blood in the control tube had hemolysed completely, whereas, Tube A contained a dark brown sediment and a lesser degree of hemolysis.

Glucosides, it will be recalled, are neutral principles, consisting of glucose combined with some other substance. A certain class of glucosides have the property of foaming when shaken in aqueous solution, and have received the name of saponins, because of their soapy appearance when treated in this manner. As we strongly suspected that such a body was the active principle, it was decided to test for the glucose molecule in the drug as follows: Five milligrams of the drug were dissolved in 3 mils of distilled water in each of 2 test tubes. To Tube 1 were added 2 drops of dilute hydrochloric acid. Tube 2 received none of the acid. Both tubes were placed in a beaker containing vigorously boiling water and allowed to remain for fifteen minutes. About 5 mils of Benedict's solution were added to each test tube after having neutralized the acid in Tube 1, and both were returned to the boiling waterbath. In Tube 1, there was a definite deposit of the red cuprous oxid on the sides and bottom of the tubes, whereas, the control Tube 2 gave a negative sugar reduction test with Benedict's solution. The hydrolysis test was repeated, and the same result obtained.

A little of the drug was added to a solution of potassium ferricyanid containing a slight trace of ferric chloride, and warmed. There was a dark precipitate of Turnbull's blue. This is another positive test for glucosides. These reactions are due to the reducing properties of glucose.

To decide the lethal dose of this substance, a rabbit weighing 2100 gm. was given intravenously 4 mg. per kilo of body weight, or 8.4 mg. (0.004 per cent of its total body weight). This was dissolved in 2 mils of saline solution. There were no remarkable effects of the drug, and the animal continued well. However, some days later, the same rabbit, weighing the same as before, received 10 mg. per kilo of body weight, or 21 mg. (0.01 per cent of the total body weight); yet nothing of interest was observed.

Thus failing to cause any toxic effects with such small quantities, the dose was raised gradually on different rabbits, and the lethal dose was found to be 208 mg. per kilo of body weight, or 499.2 mg. (0.208 per cent of the total body weight) which was 2400 gm. In about three minutes after the injection, the animal seemed quite sick and drowsy and respiration was labored. In five minutes it was seen to crouch on the floor, and would not move when jostled. The pupils were more dilated than normal and reacted rather sluggishly to light. After these observations had been made, the animal was returned to its cage. Forty-five minutes after the injection it seemed much sicker. In an hour and a half after the dose, the

rabbit was dead, and rigor mortis was generalized. An autopsy was performed immediately, and the findings were as follows:

In the examination of the eyes, the right pupil was found to be constricted; the left was apparently normal in size. The lungs were both very congested, two or three dark hemorrhagic areas being seen near the left base. There was no embolism of the coronary arteries, no postmortem clot and the oxygenated blood was darker than normal and somewhat resembled the venous blood. The liver was quite dark, spongy and hemorrhagic. The left kidney was slightly larger than the right and much darker in color, suggesting congestion or perhaps hemorrhage. There were no macroscopic findings in the spleen. The pancreas was also macroscopically negative, as was the gastrointestinal tract. The peritoneum was likewise negative. The bladder was of a purplish color and the vessels of the wall were markedly dilated. The neck of the bladder was ligated, the viscus excised and then punctured. About 25 mils of amber-colored urine was collected. It was found to contain numerous globules of a yellowish, frog-spawn-like substance which was evidently fresh mucus. This is strongly indicative of a specific action on the cystic bloodvessels and epithelium. The albumin test was strongly positive according to the heat-acetic acid method. The macroscopic findings in the lungs and liver seem to substantiate the belief that the drug is a capillary poison in toxic doses. These organs, it will be recalled, were found to be very markedly congested, even to the presence of several hemorrhagic areas.

The supposed saponin was subjected to the xanthoproteic, biuret and Millon color tests for protein and all three tests proved to be negative. No coagulable protein could be present, as all coagulable material had been removed during the process of extraction.

The dilated bloodvessels of the bladder wall of the rabbit strongly suggested that the drug might have a blood-pressure lowering effect in man, peripherally, by bringing about a dilatation of the blood capillaries and possibly of the arterioles themselves. Accordingly, the subject, aged twenty-five years, weighing 63.99 kilos, took orally 300 mg. (0.00046 per cent of the body weight), of the crude water soluble extract and within forty-five minutes, during which time normal activity was indulged, there was a change in the blood pressure from 125/72, pulse pressure 53, to 105/75, pulse pressure 30. In like manner, with body weight again the same, 20 mg. of the active principle were taken, and this time there was also a change from 119/75, pulse-pressure 44, to 105/75, pulse pressure 30. This lowering became manifest within an hour's time.

Effect on the Human Capillaries. This study was carried out with the Danzer-Hooker[1] microcapillary tonometer. The reading on the manometer scale on two separate occasions was 16 and 16.5 mm. Hg respectively; the arterial blood pressure, using the "Tycos" sphygmomanometer, was 120/80, pulse pressure 40.

Twenty milligrams of cucurbocitrin were taken by the subject in 30 mils of water, orally. Thirty minutes later, the capillary pressure by the method of Danzer and Hooker was found to be 8 and 10 mm. Hg upon two successive readings. An hour later, the blood pressure readings were taken again, and found to be only 90/75, pulse pressure 15. This reading was made with the subject in the sitting posture, after climbing three flights of stairs, and after other normal activity. There were symptoms of intracranial discomfort and drowsiness thirty minutes after the oral dose, but no headache at this time. These symptoms were followed by a dull headache about an hour later, which lasted until the patient fell asleep, about eight hours after the dose was administered.

Effect on the Capillaries of the Frog. The effect on the capillaries of 8 frogs was studied as follows:

In each case of the series 2 frogs were put under a bowl with a piece of absorbent cotton moistened with ether. In five minutes usually, they had become thoroughly anesthetized. One of these received the drug, the other being used as a control in every experiment.

The webs of the feet were immediately placed under microscopes, and invariably the capillaries were found to be tightly constricted. In the majority of the cases studied, they were so constricted, that there was no visible bloodflow whatever, while in a few, the blood corpuscles were seen to make their way with difficulty through these channels. These observations were kept up routinely for ten to fifteen minutes, after which 1 frog received an injection of 8 mg. of the drug dissolved in 1 mil of distilled water. In from ten to forty-five minutes the blood in the treated frogs began to flow quite rapidly. This was usually followed by engorgement and then stasis in the capillary bed under observation. In the control frogs, however, the capillaries usually remained tightly constricted throughout the entire observation of them, so as not to permit any bloodflow whatever, while in 1 or 2 cases, the corpuscles were seen to make their way with difficulty through the capillary network. Stretching and relaxing of the web, as being a source of error, was constantly borne in mind, and having pinned the web on the cardboard, care was taken not to disturb the specimen under any circumstances. After the blood began to flow, following the administration of the drug, several of the frogs were again subjected to ether anesthesia, and in only one instance did the capillaries become tightly constricted again. The bloodflow in the arterioles and venules was also diminished by ether, yet this was not so marked as in the capillaries.

The results on the last 2 frogs are tabulated below. Both were etherized for seven minutes, so as to render them immobile for study.

TABLE I.

Frog No.	Time observed.	Diameter of capillaries in micra before injection.	Diameter of capillaries in micra after injection.	Time injected, and amount.	Remarks.
7	8–8.10 P.M.	9.675	.....	.....	Capillaries constricted. No flow.
				10 mg. at 8.10 P.M.	
	8.15 P.M.	.....	9.675	.....	No change.
	8.25 P.M.	.....	16.125	.....	No bloodflow.
	8.35 P.M.	.....	19.350	.....	Bloodflow rapid. Re-etherized 5 minutes.
	8.45 P.M.	.....	19.352	.....	Result of re-etherization—flow slower.
8	9–9.10 P.M.	No capillaries seen	.....	10 mg. at 9.10 P.M.	No capillaries were at all visible.
	9.15 P.M.	.....	9.675	.....	Capillaries invisible until now.
	9.21 P.M.	.....	12.5775	.....	No bloodflow.
	9.30 P.M.	.....	13.8675	.....	Blood flowing slowly.
	9.35 P.M.	.....	16.225	.....	Blood flowing faster.
	10–10.30 P.M.	.....	22.575	.....	Blood flowing very rapidly.

All frogs survived these experiments in spite of the heavy doses given.

From observations on the capillaries of the human and of the frog, it was thought that there might be a small amount of histamin present in the drug, either in the free or in the combined state. There is not to our knowledge any known chemical test for this violent capillary dilator, and the physiologic test was carried out as follows:

A young virgin guinea pig about three weeks old was anesthetized with ether, and one horn of its bicornual uterus removed through a suprapubic incision. This was immediately immersed in a small beaker containing 50 mils of Ringer's solution, which had been warmed to 40° C. One end of the uterus horn was anchored to the bottom of the beaker with a 10 gm. weight, while the free end was attached by a string to a heart lever. The temperature was kept constant. ' A kymographic tracing was taken with the drum revolving at slow speed. After five minutes there was no contraction of the strip of uterus. A few drops of a 1 per cent solution of cucurbocitrin were added to the Ringer's solution in the beaker. After ten minutes no contraction occurred. Five milliliters of the same solution were added, and the drum allowed to revolve for five minutes. Still there was no contraction. The drum was stopped. After fifteen minutes it was allowed to run at the same speed. At the end of twenty minutes there was a very, very slight, almost unnoticeable rise of the heart lever, as will be seen in the accom-

panying chart, which was scarcely sufficient to call this a positive test for histamin.

Histamin, as will be recalled, or any other oxytocic, even in a dilution of this magnitude, would have produced a rather marked contraction of the strip of uterine musculature.

Effect on the Blood Pressure of Normal Dogs. There were 11 dogs in this series and a lowering of arterial pressure was obtained in 10 of these. As space will not allow, only two of these original trac-

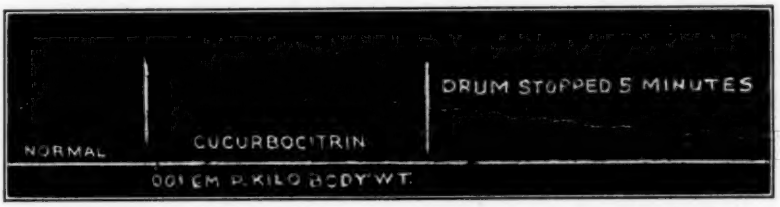

FIG. 1.—Effect of cucurbocitrin (10 mg.) on the blood pressure of a normal dog. Intravenous administration.

ings will be given (see Figs. 1 and 2). These records were routinely obtained with a glass cannula inserted into either the carotid or femoral artery with the dog under ether anesthesia. In one instance, very satisfactory results were obtained with local anesthesia, using a 2 per cent solution of novocain-adrenalin. This was a case in which the femoral artery was used as it did not necessitate the killing of the animal after the operation was finished. All of the dogs whose femoral arteries were used recovered very shortly and healing of these wounds was very rapid indeed. When local anesthesia is used there is some struggling toward the end of the opera-

FIG. 2.—Effect of cucurbocitrin (10 mg.) on the blood pressure of a normal dog. Intravenous administration.

tion due to the fact that the dog has to lie in one position for a half hour or more, rather than to pain.

The cucurbocitrin was dissolved in 1 mil of distilled water and injected into the femoral vein each time. It will be noticed from the two charts, that the blood pressure lowering effect was very different from the histamin, nitrite and proteose pepton effects, in that the lowering was gradual, slight, and indeed prolonged, all of which are to be desired when the drug is used therapeutically. The

pressures began to fall in from thirty seconds to three minutes after the administration of the intravenous dose. Again, in spite of the heavy doses received, no ill effects were noticed and all of the animals survived.

It was thought that probably the blood-pressure lowering effect might be due to a depressant or slowing action on the heart. Thereupon, a frog's heart was exposed, and its apex attached to a heart lever for a kymographic tracing. The heart itself was perfused for twenty minutes with a 1 per cent solution of cucurbocitrin, and the drum was allowed to revolve at a moderate rate of speed.

No depressant effect could be noticed, and after ten minutes, there was a slight acceleration of heart beat, due in all probabilities to lessened peripheral resistance through capillary dilatation. This could be readily brought about, as the drug could be absorbed through the serous lining of the peritoneal cavity which was open and accessible to the drug in solution. The kymograph record is given in Fig. 3.

FIG. 3.—Negative effect of perfusing frog's heart with cucurbocitrin.

Effect on Arterial Hypertension in Man. This series consisted of 10 cases of hypertension due to tuberculous nephritis. The 5 cases given in the table which follows are quite typical of the findings in the other patients. The charts of Patient No. 4 are also typical and are submitted as an example. All of the blood pressure readings given are the mean daily readings resulting from two to five determinations. In addition a few arteriosclerotic patients were used and gave very unsatisfactory results, which we cannot explain at the present time. They may be explained by the fact that the blood capillaries themselves undergo sclerotic changes, as do the arterioles and arteries.

Report of Cases. CASE I. M. L., aged twenty-four years, an iron worker, and an ex-soldier, was a heavy cigarette smoker and of a highly excitable nature, had taken strychnin and digitalis for a rapid heart and high blood pressure since his discharge from the army in 1919. He entered the U. S. Veterans' Hospital No. 41, in June, 1922, with a suspected lung lesion, which later was found to be tuberculous. Urinalysis was negative during the first three weeks of his stay in the hospital, but a moderate albuminuria began to appear intermittently after this time; this, in turn disappeared

entirely after a month. Blood pressure readings before treatment remained around 143/70; pulse pressure, 73; pulse rate, 93. This patient left the hospital against medical advice after three months, stating that he felt much better and desired to return to his work.

CASE II.—P. B., aged thirty-three years, a laborer and ex-soldier, entered the U. S. Veterans' Hospital No. 41, on April 7, 1921, with the complaint of a kidney lesion with high blood pressure dating back to 1919. The diagnosis of chronic pulmonary tuberculosis complicated by tuberculous nephritis was made. Before receiving treatment, there was a moderate hypertension of 150/110, pulse pressure 40, pulse rate 48. This patient left the hospital against medical advice in September, 1922.

CASE IV.—R. S., aged thirty-five years, a printer and ex-soldier, entered the hospital about a year previous to this observation, with the diagnosis of chronic pulmonary tuberculosis complicated by a bilateral nephritis. The urinary findings disappeared after a sojourn of about six months in the hospital, only to reappear in May, 1922. By August 16, 1922, however, the urinary picture had cleared up completely, his blood pressure was down to the normal level, and he was subjectively better.

This patient was discharged as an arrested case some time in the spring of 1923.

CASE V.—D. F. K., aged thirty-six years, an insurance agent and ex-soldier, was admitted to the hospital on August 11, 1922, with a questionable pulmonary lesion complicated by nephritis. A minimal lesion was later confirmed at the right apex. There were, also, a double plus albuminuria and hypertension of 155/110, pulse-pressure 45, pulse rate 112. This patient also had evidence of beginning arteriosclerosis. There was a history of active tuberculosis in the apex of the right lung two years previous to his admission to this hospital in 1920, which was thought to have become arrested following conscientious home treatment. He was discharged as an arrested case from U. S. Veterans' Hospital No. 41, some time during the spring of 1923.

CASE VIII.—R. M., aged twenty-eight years, an automobile mechanic and ex-soldier, entered the hospital in August, 1922, for observation as to the cause of his high blood pressure. There was no pulmonary lesion, but his symptoms and urinary findings pointed to a nephritis, probably tuberculous. Initial blood pressure readings were found to be around 135/88, pulse pressure 47, pulse rate 65. This patient was discharged from the hospital some months later, and returned to his work.

The results of treatment are shown in the following table and charts:

TABLE II.—MEAN BLOOD PRESSURE DETERMINATIONS.

Patient, No.	Before treatment.					On treatment.					Remarks.
	Day.	Systolic.	Diastolic.	Pulse pressure.	Pulse rate.	Day.	Systolic.	Diastolic.	Pulse pressure.	Pulse rate.	
1. Age 24	1	143	70	73	93	1	119	50	69	84	Blood pressure within normal limits while drug was being taken.
	2	140	50	90	91	2	137	50	87	82	
	3					8	122	76	46	76	
2. Age 33	1	150	110	40	48	1	132	86	46	59	Three doses administered. Blood pressure within normal limits for three weeks afterward.
	2	135	76	79	62	2	124	75	49	60	
						3	119	59	60	75	
						4	111	51	60	66	
4. Age 35	1	158	105	53	76	1	119	74	45	77	Blood pressure was normal during treatment; duration of blood pressure lowering was about ten days after stopping treatment.
	2	140	95	45	90	2	128	77	51	88	
						3	140	95	45	76	
						9	129	83	46	87	
						10	126	76	50	82	
						11	124	76	48	85	
5. Age 38	1	158	88	70	110	4	131	90	41	93	This patient had beginning arteriosclerosis. Lowering was not manifest until he had been on treatment four days. Blood pressure rose after withdrawal of drug.
	2	155	80	75	112	5	134	92	42	82	
	3	139	95	44	98	6	120	93	27	93	
8. Age 26	1	145	90	55	65	1	124	69	55	72	Blood pressure never ran above normal during the three weeks this patient was under observation.
	2	140	87	53	66	2	119	74	45	68	
						3	139	82	57	84	
						4	124	80	44	82	
						5	120	63	57	76	

Effect of Treatment on Acute Cystitis. Report of a Case. CASE X. —T. P., aged twenty-four years, suffering from chronic pulmonary tuberculosis, was referred to the urologic clinic for the treatment of gonorrheal urethritis. The routine treatment with acriflavine and mercurochrome was instituted. Two weeks later he com-

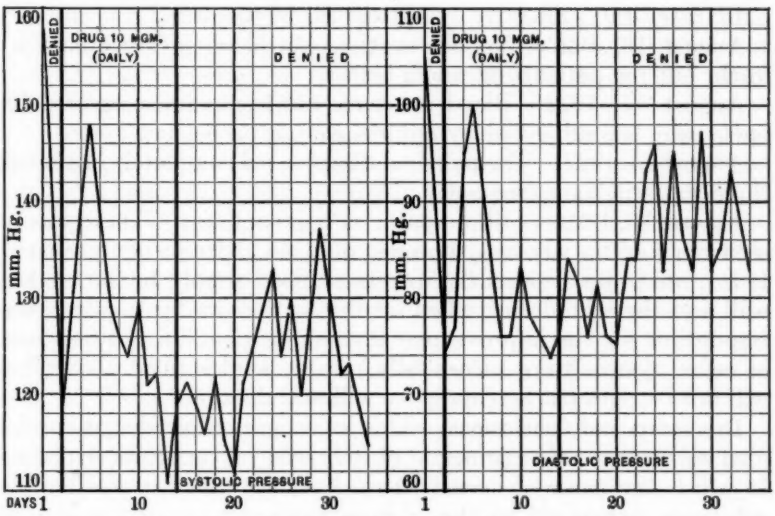

FIG. 4.—R. S. (Case IV). Daily blood-pressure readings.

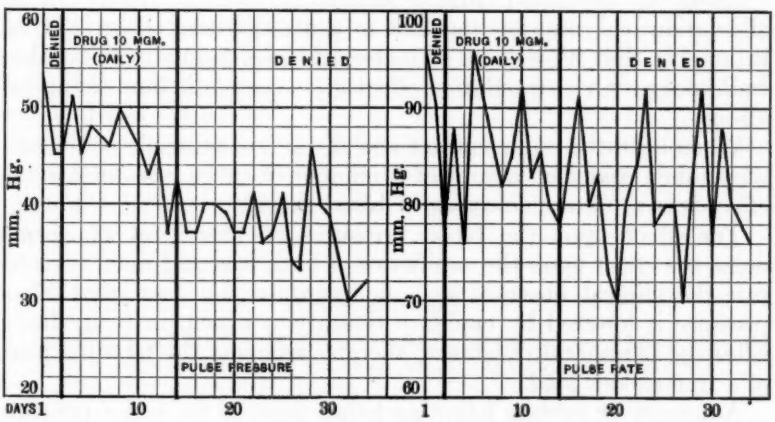

FIG. 5.—R. S. (Case IV). Daily mean pulse-pressure and pulse-rate chart.

plained of sharp pains over the bladder and frequency of micturition. There was slight elevation of temperature and pulse rate above that of chronic pulmonary tuberculosis, and a diagnosis of acute gonorrheal cystitis was made from his history and symptoms. The patient's initial blood pressure was 114/85, pulse pressure 29,

and pulse rate 90 on August 10, 1922. With the hopes of bettering his condition, he was directed to take 10 mg. of cucurbocitrin at 10 A.M. and 9 P.M. for five days. The clinical course was as follows:

August 11, 1922. Blood pressure, 105/65; pulse pressure, 65; pulse rate, 100; pains much less severe, though still some frequency.

August 12, 1922. Blood pressure, 112/70; pulse pressure, 42; pulse rate, 100; subjective symptoms about the same.

August 13, 1922. No observations on blood pressure, and so-forth; but the patient felt much better.

August 14, 1922. Blood pressure, 110/58; pulse pressure, 52; pulse rate, 96; subjective symptoms were even better.

August 15, 1922. The pain had disappeared completely, although there was still some frequency.

August 16, 1922. Still no pain. Frequency less. There was no recurrence of the above symptoms, only slight frequency persisted. It is quite probable that the increased blood supply to the bladder wall and the stimulating effect on the epithelium by the drug was responsible for the improvement in the cystitis Three other cases of acute cystitis were successfully treated as described above, but will not be reported here as space will not allow.

Discussion and Conclusions. This investigation of what is considered to be the active principle of the seed of cucurbita citrullus, to which the name of cucurbocitrin has been given, is evidently a substance belonging to the glucoside-saponin group manifesting certain pharmacological actions worthy of further study.

There is a historical clinical background for this remedy in the alleviation of symptoms incident to acute cystitis. Its use seems rational in that it produces an increased blood supply to the bladder wall, along with a stimulating effect upon the epithelium lining this viscus.

When both the crude extract and the active principle of the seed were taken orally by a subject a number of times, the outstanding effect was a prompt lowering of blood pressure.

The effect upon the blood pressures of 10 out of 11 normal dogs, the effect upon the capillaries of both frog and man, corroborate the clinical observations, and point to the fact that blood pressure is lowered by capillary dilatation, which, in turn, diminishes the peripheral resistance, thereby relieving the laboring heart of a tremendous load.

Autopsies on rabbits following lethal doses of the active principle showed congestion and hemorrhages of lungs, liver and kidneys, and, an observation that seems to be of particular significance, marked dilatation of the bloodvessels of the bladder wall, with a coincident enormous flow of mucus bathing the cystic mucosa, suggestive of selective action by the drug.

With clinical trials in a limited number of cases of moderately increased blood pressure in the human, we obtained a lowering in

both systolic and diastolic pressures with a corresponding lowering in the pulse pressure in most of the cases studied. The pulse apparently becomes more stable, and the patients experienced greater comfort; some of them were able to tell when the pressure was rising after the drug had been denied for a few days.

In 4 cases of acute cystitis, which were treated with the drug, the clinical relief was very prompt.

Histamin, either in the free or combined state, is no doubt absent from the active principle, as the physiologic test on the virgin guinea-pig uterus was negative.

No attempt has been made in this paper to fully explain the pharmacologic action of the drug, and the paucity of clinical material herewith presented is fully realized. However, further studies are in progress, the results of which will be presented in future papers.

In all of the clinical trials, no ill effects were noticed, and for this reason, the drug cannot be considered toxic even in very large doses. It possesses a rather slow and prolonged action. The results in the presence of pronounced arteriosclerosis seem to be very slight, and at the time we cannot account for this. An insufficient number of cases of senile hypertension is a possibility, and further work on these patients might prove encouraging.

The usefulness of this drug is suggested in cardiorenal conditions, and perhaps the other forms, also to the probable specific relief of acute and chronic pathology of the urinary bladder, in that the bloodvessels of the bladder wall become dilated, thereby increasing the concentration of antibodies to combat the invading organism, and for the increased amount of food and oxygen for subsequent repair at this seat of infection. It will be recalled that wounds of the face have a tendency to heal very quickly due to the rich blood supply of this region.

I am very grateful to the following for their valuable assistance and suggestions: Drs. Oliver T. Osborne, L. B. Kline, Francis B. Johnson, J. H. Cannon, L. H. Prince, Robert Wilson, F. P. Underhill, and George E. Barksdale.

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REVIEWS.

MODERN MEDICINE: ITS THEORY AND PRACTICE. Edited by SIR WILLIAM OSLER, BART, M.D., F.R.S. Third edition, thoroughly revised. Reëdited by THOMAS MCCRAE, M.D., Professor of Medicine in the Jefferson Medical College, Philadelphia. Vol. I. Pp. 845; 58 illustrations. Philadelphia: Lea & Febiger, 1925. Price, $9.00.

A THIRD edition of a "System of Medicine" is indeed a *rara avis*. The publication, then, of this Volume I constitutes an important event in American medical literature and calls for congratulations to publishers, editors and authors. Twelve years have elapsed since the appearance of the second edition, and eighteen since the first, which therefore stands about midway between this volume and Pepper's "System." Such is the rapidity of medical advance that Pepper's "System" had already become of historical interest only when *Modern Medicine* first appeared, and in the same way the need for another edition of the latter was annually becoming more apparent. Nevertheless we are glad that the editors have seen fit to include the author's Introduction on the Evolution of Modern Medicine, which had been omitted from the second edition. Like so many of Osler's writings, it is perennially fresh and starts the reader in the way in which he should go to such good effect that it is well worth its twenty pages. The first volume has been shortened by over two hundred pages by omitting the diseases of doubtful or unknown etiology—still no inconsiderable list—and by a steady though slight condensation of most of the chapters. The "new disease," tularemia, is included and scarlet fever lifted from the ranks of doubtful causation. In future volumes sections on botulism and epidemic encephalitis are promised; diseases of the esophagus will be discussed by men who have observed visually their field of work; insulin and metabolism are to be given especial attention. Evidences of conscientious and successful attempts to bring the subject matter up to the latest date are too numerous to mention, but glances at the footnote references will show how many are from the last decade and even from the last two or three years. It is to be regretted that they are not more numerous, and that so many are incomplete in the bibliographic sense. In the chapter on Influenza, which has necessarily been considerably altered, it is

interesting to note that Lord strongly favors Pfeiffer's bacillus as the causative agent. Only one misprint has been observed thus far: that Marmorek found streptococci in scarlet-fever throats in 1825 (p. 747). E. K.

A LABORATORY GUIDE IN GENERAL ZOÖLOGY. By A. RICHARDS, Professor of Zoölogy, University of Oklahoma. Pp. 149. Philadelphia and New York: Lea & Febiger, 1925. Price, $1.75.

IN a laboratory guide in general zoölogy one does not expect to find a systematic treatment of the subject. The plan must include certain well-recognized pedagogic principles, such as proceeding from the known to the unknown and introducing the subject with an animal large enough to be studied without a microscope.

The laboratory guide before us shows a mature grasp of these principles. This is not strange, because the *Guide* is the result of an evolution through several typewritten editions and then through three privately printed editions, extending over a period of thirteen years.

The plan is original, and consists of three parts: Part I gives the principles of morphology and physiology, beginning with the frog, passing to the protozoa, hydra, earthworm and crayfish. Part II deals with the principles of animal biology. Here such general subjects as cell division, embryology, metabolism, genetics, ecology, taxonomy and distribution are treated. Part III, The Animal Kingdom, includes those phyla not covered in Part I, and so represents a general survey of the animal kingdom.

The *Guide* deals with certain factors in evolution, such as animal distribution, but homology and paleontology, which lend themselves so well to laboratory treatment, are notably absent. Perhaps this can be accounted for by the fact that Oklahoma has an anti-evolution law. The book is well printed and carefully written.

H. C.

TEXTBOOK OF NERVOUS DISEASES. By CHARLES L. DANA, M.D., Professor of Nervous Diseases in Cornell University Medical College. Tenth edition. Pp. 667; 262 illustrations. New York: William Wood & Co., 1925.

THIS book, intended primarily for students and practitioners of medicine, is a short account of the most common diseases of the nervous system. In this edition a chapter on the "History of Neurology,' by Fielding H. Garrison, covering forty pages, is one of the worth-while additions. For the most part the description of the various subjects is well done, but many misprints occur that were

also present in the ninth edition. For example, Fay-Sachs disease instead of Tay-Sachs (p. 424); tender joints instead of tender points (p. 204); ognococcus instead of gonococcus, and so on. The reviewer feels that the word neurosis should not be applied to conditions that have organic lesions and that brachial paralyses and other such conditions should not be classed under the heading of Neuroses of the Motor Spinal Nerves, as is done in this book.

Despite the rather numerous typographic errors, and the rather doubtful correctness of classification alluded to, the book can serve a good purpose by giving students a quick and broad conception of the nervous diseases that are met with in daily practice.

N. W.

EMPYEMA THORACIS. By EVARTS A. GRAHAM, M.D., Professor of Surgery, Washington University, School of Medicine. Pp. 106; 13 illustrations. St. Louis: C. V. Mosby Company, 1925.

THIS volume is a consideration of the principles governing the treatment of empyema. It is based on impressive research on the effect of pneumothorax in animals and cadavers and on clinical experience with the Empyema Commission of the United States Army. A new conception of the pathologic physiology of pneumothorax constitutes the most important part of the study. Clinical treatment of empyema of the hemolytic streptococcus variety, based on this conception, reduced the mortality from this condition enormously.

The exposition of the subject is brief, pleasing and convincing.

W. B.

CLINICAL THERAPEUTICS. By ALFRED MARTINET, M.D., Paris, France, with the collaboration of ten physicians. Authorized English translation from the second revised and enlarged edition, by LOUIS T. DEM. SAJOUS, B.S., M.D., Associate Professor of Experimental Pharmacology, School of Medicine, Temple University; Instructor in Endocrinology, Graduate School of Medicine, University of Pennsylvania, Philadelphia. Pp. 1800; 332 illustrations in two royal octavo volumes. Philadelphia: F. A. Davis Company, 1924.

THE work has four subdivisions: Part I, entitled "Therapeutic Agents," is devoted to a discussion of the mode of action of, indications for and use of drugs, dietary measures, the various types of physiotherapy and psychotherapy. In Part II are described the technics of common therapeutic procedures, such as lumbar puncture, paracentesis of the serous cavities, intravenous injections,

cupping and the like. Part III, called "The Treatment of Symptoms," gives a series of individual symptoms, which are alphabetically arranged, with a discussion of the therapeutic indications. Part IV takes up the treatment of particular diseases.

The work contains a wealth of valuable therapeutic information, but its scope is so broad that it has of necessity become shallow and inadequate in places; for example, diets in the vitamin deficiency diseases. In his introduction the author remarks that the aggregate of therapeusis up to the Nineteenth Century may be summed up as "a pile of rubbish and a handful of jewels," and refers to his difficulty in deciding how much to include. He has erred in the direction of too much rather than too little (for instance, the oral administration of preparations of horse chestnut for varicose veins!), and shown a tendency to the polypharmacy of a generation ago. The American reader will be surprised at the advice of temporizing measures under certain circumstances in acute appendicitis. The work of the translator has been very well done; in many instances his parenthetic additions have brought the original up to date, as in the case of insulin therapy in diabetes. R. K.

THE HISTOLOGY OF THE MORE IMPORTANT HUMAN ENDOCRINE ORGANS AT VARIOUS AGES. By EUGENIA R. A. COOPER, Victoria University of Manchester, England. Pp. 106; 61 illustrations. Oxford: Oxford University Press, 1925.

THIS small book is a study of physiologic variations due to age alone in the anatomy (chiefly microscopic) of the pituitary, thyroid, parathyroid and thymus glands. The study begins with early intrauterine life and ends with old age. The material was necessarily from postmortem subjects, but changes due to disease and postmortem influences were guarded against by careful selection.

The style is lucid; the illustrations well selected and technically very good. The description of age variations should serve a very useful purpose in preventing investigators from attributing such to pathological processes. These changes, however, appear from this work to be usually less important than those occurring from similar causes in the breast. The book seems more important as a contribution to the normal histology of organs inadequately described in the average textbook.

It is to be regretted that a consideration of differences in these endocrines (if any) due to sex was not given to this material. A mention of the number of cases examined in the various age periods would have made the conclusions more convincing.

W. B.

THE LIFE OF SIR WILLIAM OSLER. By HARVEY CUSHING, M.D. Two volumes. Pp. 1413; 43 illustrations. Oxford University Press, 1925.

THE reviewer finds himself under the spell and charm of this man that was Osler. Known to him before only in the *Textbook* and *A Way of Life*, in scattered journal articles, *Æquanimitas* and *An Alabama Student*, and admired as clinician and philosopher, he has become to the reviewer in these pages a living personality to be loved and revered.

Wherein lay Osler's greatness? Many and valuable as were his contributions to medical knowledge, one can point to no outstanding scientific discovery of his that will loom large in medical history. Of his contemporaries, some were equally skilled in the medical art; others were as brilliant as teachers. It was something less tangible, less ponderable than these. It lay rather in the great humanity of the man; in a personality and character that inspired all with whom he came in contact in his many-sided life. But such greatness may be lost in a generation with the passing of those whom the man directly or indirectly influenced, unless some inspired brush can forever fix to canvas the fleeting picture before time and forgetfulness blur and erase its details. The author has admirably succeeded. "Merely the outline for the final portrait," says the author, yet how deftly drawn!

That some minor errors should have crept in was inevitable; it is surprising that they are so few. The reviewer calls attention to the founding of the AMERICAN JOURNAL OF THE MEDICAL SCIENCES in 1820, not in 1827 as stated on page 276.

The work should have a universal interest, a catholic appeal. To students: That they may know him who "made it possible for them to work at the bedside in the wards;" who throughout a long, fruitful life was always the eager student and the "young man's friend." To teachers: Because of the indelible mark he left on medical education and the leading role he played in an important period of medical progress—who was, wherever he went, the "potent ferment," "the angel who stirred the pool." To all physicians: That they may know familiarly the life of one of the greatest physicians of all times, and through him something of the glorious history and tradition of their profession; that they may find a fresh idealism and a new inspiration in his example. To the non-medical reader: For here the story of a wonderful life is charmingly told.

R. K.

PROGRESS

OF

MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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Sudden Death Due to Exacerbation of Latent Syphilitic Myocarditis.—The first number of a new journal (*Am. Heart J.*, 1925, **1**, 1) devoted to the diseases of the heart has just made its appearance. The purpose of this journal, as outlined by the Editor-in-Chief, Dr. Lewis A. Conner, is twofold: (1) To supply a periodical covering the field of the diseases of the heart and circulation, and (2) to supply an organ for the dissemination of the objects and purposes of the American Heart Association. The future of this new journal promises well, judging from the quality of the material, the close editorial supervision and the excellent mechanical reproduction of material in the first number. It might be of interest to detail briefly the articles that appear in the journal and to comment briefly on each of them, as an indication of the type of material which is presented and the character of the work in general. The first article, by WARTHIN, deals with a hitherto unrecognized cause of sudden death which is characterized by the rapid onset of marked symptoms of cardiac insufficiency in apparently healthy individuals. Death in these cases occurs without evidence of valvular lesion, without the usual history of antecedent disease which produces valvular lesions, but with the history of syphilitic infection, developing in young and middle-aged males and instigated apparently by overexertion and heat. In these cases the author has found present in the myocardium large numbers of spirochetes and polymorphonuclear infiltration and marked edema, which he likens to the "critical reaction" which occurs in experimental syphilis in animals as described by Brown and Pearce. The next article, by LIBMAN, discusses the prognosis in subacute bacterial endocarditis. The author

divides these cases into five different types: (*a*) The unusual, (*b*) bacteria-free, (*c*) transitional, (*d*) mild, and (*e*) recurrent. Each of the different types is discussed rather briefly, and from the study of these several types he draws the conclusion that these cases may exist for a long period of time, may recur, occasionally recover spontaneously and in the course of healing chronic valvular disease is produced. LEVINE and NEWTON bring out some interesting observations on the selection of patients with angina pectoris for sympathectomy. They believe that if the right type of patient is selected, without myocardial weakness and preferably without valvular disease, that much can be done to help a patient by this operation. The next article is an economic discussion of cardiac disease by CARR, and is well worth reading. WILLIUS and HAINES, in a short article report on 162 cases of high-grade myxedema, in which they were unable to find any evidence of cardiovascular disease attributable to the myxedema. BRADBURY and EGGLESTON report a very interesting syndrome occurring in 3 patients in which there was marked lowering of blood pressure as a result of changes in posture. They are unable to explain the mechanism of the production of this change, but suggest that it may be due to some disturbance in functional activity of the vegetative nervous system. WHITE and MEYERS outline a method of classification of cardiac diagnosis, and state that every case should have in the diagnosis three features—cause, structural changes and functional ability of the heart; for example, cardiac enlargement and auricular flutter of unknown cause, able to carry on slightly curtailed activities. KERR and METTIER next discuss the circulation of the heart valves and with India-ink preparations of injections of the valves they show that these structures are vascularly very rich, confirming the embolic conception of endocarditis. MCLEAN'S paper deals with methods of lessening heart disease which could be made official. The concluding paper of this new journal describes a new electrode for clinical experimental electrocardiography, as devised by HERRMANN and WILSON. This new electrode is of value not only in the handling of patients, but has a very definite value as an electrode in experimental work on animals.

SURGERY

UNDER THE CHARGE OF

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The After Results of Operations for Malignant Disease of the Breast.—PERRY (*Brit. Jour. Surg.*, 1925, p. 1339) states that operation has justified itself when it is found that 28 per cent of all cases survive

more than seven years. The most favorable age for operation is the quennium, fifty to fifty-four years, both as regards duration of life and also as regards recurrence being delayed for a more lengthy period. In young patients the prognosis is not so good and recurrences are more likely to occur early. The absence of deposits of carcinoma in the axillary glands improves the prognosis, and it is possible that the microscopic evidence of chronic inflammation suggests an increased resistance to the disease. Medullary carcinoma is not such a fatal disease as it is so frequently considered. Cases showing carcinomatous hyperplasia should be regarded as definitely malignant and a radical operation performed. Papillary cystic and intracystic carcinomata are the least malignant and intraductular carcinoma is only slightly more so. Late recurrences do not occur even as long as fifteen years after operation. This possibility almost precludes the establishment of a cure in malignant disease of the breast. All operations must be thorough and one would be inclined to extend the operation still further by removing the supraclavicular glands. There appears to be no grounds for believing that the lower inner quadrant of the breast is a dangerous area for cancer origin.

Noncarcinomatous Tumors of the Stomach.—MEYER and BRAMS (*Surg., Gynec. and Obst.*, 1925, **41**, 311) say that a series of noncarcinomatous tumors of the stomach is reported, consisting of one myofibroma, two polyps, one adenoma *en nappe* and one hypertrophic pyloric stenosis in an adult, and mention is made of certain inflammatory conditions, namely, syphilis of the stomach and inflammatory pancreatitis associated with chronic peptic ulcers. The importance in recognizing these conditions consists of the fact that operation, except in syphilis of the stomach, is the only procedure which can cure the patient. Even syphilis of the stomach may require surgical aid if the symptoms of obstruction are severe, or if marked connective-tissue scar stenosis has developed. The nonmalignant tumors of the stomach, especially the myomata and polyps, may undergo malignant degeneration in a large proportion of the cases and early radical removal is the only logical method to prevent this complication. Polyps and myomata may cause severe or fatal hemorrhage or occlusion of the pylorus or duodenum with alarming symptoms. Recognition of these tumors and prompt surgical treatment may not only cure the conditions, but may also prevent the occurrence of serious complications sometimes caused by benign growths of the stomach.

A Clinical Study of Some Common Anatomic Abnormalities of the Colon.—KENTOR (*Am. J. Roentgenol.*, 1925, **14**, 207) states that low cecum is a common congenital anomaly of the colon occurring in 18 per cent of all patients. This anomaly occurs more often in persons of the asthenic habitus and is more common in women. Patients with low ceca show a marked tendency to present certain reflex or toxic symptoms. Most of them vomit and many suffer from headache. The exact nature of this association between low cecum and the symptoms described is not yet clear. Attention is thus invited to the colon as a factor in vomiting a hitherto insufficiently emphasized concept. The presence of low cecum can be diagnosed positively only

by Roentgen examination. Appendectomy is usually performed, but is seldom of benefit in cases of low cecum. Appropriate conservative medical treatment gives relief, a cure in the great majority of cases.

Renal Tuberculosis.—PERSSON (*Ann. Surg.*, 1925, **82**, 526) says that his cases show that the frequency of renal tuberculosis in men is almost twice that in women. Hereditary tendency can be traced in 25 per cent of the cases. Almost two-thirds of the cases are patients in the third or fourth decades of their lives. The cases of localization to the right kidney exceed those of the left. Coincident tuberculosis in other organs has, according to the records, been shown in about half of the cases. Bladder irritability has been found as an initial symptom in 74 per cent of the cases, pains in the kidney region in 18 per cent, while serious hematuria was noted in 5 per cent. Absence of albuminuria has been noted in 7 patients. Pyuria has never been absent. Tubercle bacilli have been demonstrated in 85 per cent of the cases. The extent and grade of the bladder tuberculosis seems to have exercised a considerable influence on the final result of the operated cases. In slight ulcerations of the bladder the late mortality has been almost three times greater than when such have been absent. In extensive ulcerations the mortality has been extremely great.

Bladder Neoplasms.—MACKENZIE (*J. Urol.*, 1925, **14**, 275) writes that one finds a great diversity of opinion both as to pathology and methods of treatment. There are many classifications of these growths and many ways of dealing with the subject. The majority of primary tumors of the bladder are of course the papillary fibroadenomata and the papillary villous cancers. Besides these, squamous-celled cancers, with epidermization, and cylindrical-celled cancers are at times noted. Of other tumors, fibromyomata sometimes with other connective-tissue additions and large, sometimes papillary nodular-sarcomatous myomata of either smooth or striated muscles occur. Much rarer are the ordinary small round-celled sarcomata, spindle-celled sarcomata and very rarely lymphosarcomata and osteosarcomata. Of these groups the epithelial tumors are most important. Hematuria is the chief complaint in these cases. Frequency of micturition and dysuria follow. Pain in the loin, incontinence, pain in the perineum and genitalia are fairly common associated symptoms. The importance of blood in the urine cannot be overestimated. The examination of the prostate is of equal importance. The age and development of the growth must be definitely settled. Freer and more open surgical methods, even in cases of recurrence, must be followed.

Davis Method for Closed Reduction of Congenital Dislocation of the Hip.—DICKSON (*J. Bone and Joint Surg.*, 1925, **7**, 873) says that Dr. G. G. Davis, of Philadelphia, described a method for the reduction of congenital dislocation of the hip, which he named the "push method." It may be considered a combination of the direct and circumduction methods. The results in 24 hips reduced by the Davis method were: 21 out of the 24 were reduced, giving a percentage of 87.5 successful reduction. Of the 21 hips reduced, in 3 the results have not been satisfactory. The author feels that these results as to reduction and

outcome compare favorably with those of other methods of closed reduction. He feels that there is less danger of producing a fracture of the femur than in most of the circumduction methods, as the force is applied to the head of the bone, no leverage action being used. There is a minimal amount of trauma to the soft part by this method. The sooner after the age of two years the hip or hips are reduced, the better are the results. The closed reduction after the age of seven years is difficult and the outcome as a rule far from satisfactory.

A Manometric Study of the Cerebrospinal Fluid in Suspected Spinal Cord Tumors.—STOOKEY and others (*Surg., Gynec. and Obst.*, 1925, **41**, 429) state that in suspected spinal cord neoplasms manometric readings of the cerebrospinal fluid through lumbar puncture should be a routine procedure. Manometric studies of the cerebrospinal fluid through lumbar puncture (without cistern puncture) may indicate complete subarachnoid block, incomplete subarachnoid block or the presence of a free unobstructed subarachnoid space. In all patients operated upon in whom the manometric tests indicated complete subarachnoid block some form of spinal cord neoplasm was found. In all patients in whom the manometric tests indicated incomplete subarachnoid block either a spinal-cord neoplasm or some other form of subarachnoid block was found. Negative manometric readings were found in 2 patients having an early symmetrical enlargement of the cord, presumably an intramedullary tumor which, however, did not interfere with the free circulation of the cerebrospinal fluid. In all others exposed the manometric findings were substantiated at operation. Combined lumbar and cistern puncture is indicated when manometric studies through the lumbar puncture alone do not permit of definite conclusions being drawn. In the author's experience combined lumbar and cistern puncture was indicated in only 3 cases out of 50 suspected spinal-cord tumors.

Articular Surfaces in Tuberculous Arthritis.—PHEMISTER (*J. Bone and Joint Surg.*, 1925, **7**, 835) claims that in the earliest stage the articular cartilage is usually destroyed most extensively along its free articular surfaces by granulations which overgrow it from the surrounding synovial membrane. In the regions of contact and pressure of articular surfaces surface destruction by granulations does not take place and the cartilage is preserved longest. As the disease progresses subchondral granulations develop which absorb articular cortex and attack the cartilage from beneath. In severe tuberculous arthritis there may be early necrosis and caseation of the overgrowing synovial granulations, so that there is little or no destruction of articular cartilage along its free surface. In this event the destruction of articular cartilage is brought about mainly by subchondral granulations, which do not undergo early necrosis and caseation and do not present the usual histologic picture of tuberculous tissue. The bony involvement along the articular surface may be either primary or secondary. When primary the dead bone may break down, leaving a cavity or may persist and form a sequestrum which has articular cortex and in some instances cartilage preserved on it and is denser than the surrounding living bone, which subsequently atrophies. Secondary involvement

of the bone along the articular surfaces may lead either to destruction of the entire articular cortex by superficial caries or to more or less extensive and deep areas of necrosis at the points of greatest pressure in the joint.

Tumors of the Small Intestines.—Lin (*Arch. Surg.*, 1925, **11**, 602) states that the lymphoblastoma is the commonest tumor in the small intestine. Spindle-cell sarcoma of the small intestine has never been observed in the Johns Hopkins Laboratory. Males are more susceptible to all tumors of the small intestines than females. The adenoma occurs in persons under thirty years and carcinoma in those over thirty-five years. The lymphoblastoma may occur at any age, but a large proportion, over 40 per cent, are in children under ten years of age. Carcinoma infiltrates early and gives rise to annular growths. Adenoma does not infiltrate and is usually polypoid. The lymphoblastoma may be either annular, polypoid or fungoid, but the form of the growth in the latter bears no relation to the tumor's malignancy. Carcinoma is usually single, adenoma often multiple. Intussusception frequently accompanies tumors which are polypoid or fungoid, being present with almost all in this series either benign or malignant. Only a small percentage of the annular tumors are thus complicated. Stenosis is the rule in all annular tumors. The adenocarcinoma is always malignant, the adenoma always benign. The lymphoblastoma may be either benign or malignant, and there is no possible way to tell whether a tumor of this nature will recur or not even from careful study of microscopic sections.

PEDIATRICS

UNDER THE CHARGE OF

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Thymus and the Treatment of Its Hyperfunction.—DeBuys, Samuel and Bowie (*J. Am. Med. Assn.*, 1925, **85**, 1551) state that up to the present time that they have been unable to arrive at a definite standard as to the size, shape and position of the gland causing symptoms, some patients having all the effects of a hyperfunctioning thymus, and on examination showing only a very slight enlargement, while other cases in this series with marked enlargement of the gland showed no clinical symptoms. The heart shows no relationship in size to the thymus, although usually with a marked thymic enlargement there is an increase in the size of the right side of the heart. In a large percentage of these cases the shadow of the thymus is seen to the right and to the left, with the large finger-like projection overlying the right side of the heart. In treating the choice must be made between radium and Roentgen-ray irradiation. In the application of the rays to children, theoretically the use of radium is preferable, as it can be fixed

firmly in place, and no matter how restless the child may be the rays are constantly directed to the region of the gland. In using radium their method is to use 100 mg. of radium element in 2 mm. of brass filter, separated from the skin by a distance of 5 cm. firmly fixed in place by adhesive plaster reinforced by a binder. The duration of the exposure has varied from eight to twelve hours, depending on the urgency of the case and the size of the thymus, as well as the age and the size of the child. Anterior application has been made as a rule, although in giving a series of three radium exposures the second dose has been applied posteriorly. The interval between applications has usually been from ten days to two weeks, unless the condition of the child is grave. Three applications with no improvement has been the limit of its use. The success has been quite uniform, and rarely have more than three or four applications been necessary. No ill effects were observed. Their Roentgen-ray dosage, which is their method of choice, may seem rather mild, but they seem to get the results. They give one minute exposure, 7 inches gap, 5 ma., 1 mm. of aluminum filter, 10 inches distance; this giving approximately one-tenth of a skin unit. The number of treatments required is determined primarily by the clinical symptoms and to a secondary degree by the size of the thymus, as shown in the roentgenogram. No bad effects have been noted following the treatments. The only difficulty attendant on the Roentgen-ray irradiation of the thymus has been the restlessness of the patient, but it has always been possible in some way to hold the child still for the length of the treatment. The average number of exposures required is from four to five. Out of a total of 623 cases of children irradiated at various ages, from birth to thirty-nine months, 125 cases of thymic enlargement have been observed, which is about 20 per cent. The length of time these cases have been under observation has varied greatly, owing to the difficulty of retaining clinical patients under observation.

Comparison and Interpretation on a Caloric Basis of the Milk Mixtures Used in Infant Feeding.—Powers (*Am. J. Dis. Child.*, 1925, **30**, 453) brings out the following points for emphasis in his study: The dilution of the milk mixtures with water affects the calories per unit of mass, but not the percentage relationships of protein, carbohydrate and fat in the total calories. The addition to milk mixtures of an energy-yielding nutrient affects no only the total calories per unit of mass, but also diminishes the proportional representation in the total calories of the protein, lactose and fat. The magnitude of any food component in a mixture, as expressed by its percentage representation in the total calories, is relatively increased by the removal or reduction of any other food component. On the other hand, an energy-yielding nutrient, if introduced in a ratio fixed with relation to the total constant volume of mixtures made increasingly dilute with water brings about a reduction in the values of the protein, lactose and fat percentages of the total calories. When the multitude of milk mixtures commonly used in infant feedings are reduced to the caloric percentage formulation it is perceived that many of them are essentially alike or identical excepting in concentration, degree of denaturization

by cooking, souring and qualitative differences in protein, carbohydrate, salts and fat. Practically all mixtures may be found in one of seven groups. A great number of mixtures which experience has shown to be particularly successful in feeding infants fall into a majority group which approaches the caloric percentage pattern of the food mixtures in the sweetened condensed milk group; about 60 per cent of the total calories are in whole milk and 40 per cent in added carbohydrate. One-third milk with 5 per cent of added sugar, and somewhat less frequently-used mixtures, have the same caloric percentage configuration of sweetened condensed milk and of whole milk to which 17 per cent of sugar has been added. Human milk, cows' milk, whey, protein milk and skimmed milk are the most important representatives of the other groups. The Czerny-Kleinschmidt and Moro butter-flour mixtures have the same proportions of the total calories in protein, carbohydrate and fat as human milk. It is a striking fact that the vast majority of successful milk mixtures used in infant feeding are unlike human milk, which stands apart from all other foods. The popular artificial mixtures are as unlike human milk as they are unlike unmodified cows' milk.

Light and the Antirachitic Factor.—Block and Faber (*Am. J. Dis. Child.*, 1925, **30**, 504) state that the clinical investigations hitherto made on the action of light on rickets are not all entirely sound and straightforward. In many instances the experimental conditions before and during the light treatment were not uniform, so that the possibility arises that other factors than the light have exerted an influence. The same thing applies to the research concerning the action of light in tetany. They have had an accurate measure of the intensity of rickets in the phosphorus determination and of the degree of tetany in the calcium determination so that they felt justified in undertaking an investigation into the effect of light on patients with these diseases. These were made during the autumn and winter seasons, during which there is not much sunlight in their country, and when these conditions do not improve spontaneously. The diet consisted of milk and carbohydrates. It was about the same before, during and after the light treatment, and it was usually the same diet as that of children who were ill. No cod-liver oil preparation was given which might affect the disease. The only change was exposure to the mercury-quartz light every other day, beginning as a rule with five minutes daily. The blood phosphorus and calcium were estimated after eight hours' fasting. They have determined the phosphorus and calcium content of the blood in about fifty children, all of whom exhibited the characteristic clinical signs of rickets or tetany or who had both diseases at the same time. The blood phosphorus was restored to normal under the influence of the quartz light. This effect occurred within a month after a total exposure of about one hundred minutes. How soon the effect begins is not at present known although it surely varies, depending on the severity of the case. These investigations proved that it is the light alone that causes the blood phosphorus to rise and as it remains present in normal amount even when the exposure to the rays has been discontinued after a few exposures, this stable

condition cannot be due to the fact that the light has contributed or liberated a missing substance, be it phosphorus or a vitamin, because these bodies are constantly used up in growth, and a new supply must therefore be furnished. It is more likely that a depressed function is revived by the action of the light. The majority of investigations have shown that the mercury-quartz light has the same curative value in tetany, the concentration of the blood calcium rising from subnormal to normal as a direct result of the light treatment. In all the cases treated by the authors a marked effect on the blood calcium was observed with an almost instantaneous cure of the disease in less than two weeks. Ultraviolet light thus acts on tetany just as it does in rickets. After a few exposures the amount of calcium in the blood rises to normal, but it cannot be made to exceed this, and even before this has happened all clinical signs of the disease have disappeared. Clinically tetany is soon cured by light treatment, while rickets disappears gradually, which is a natural consequence of the fact that the soft bone tissue requires some time to calcify. It is interesting to note that the blood calcium will remain normal, even if the exposure to the rays is discontinued; in fact when it has started to rise it continues to do so irrespective of whether the child is treated or not.

The Chemical Composition of the Spinal Fluid.—Wilcox, Lyttle and Hearn (*Am. J. Dis. Child.*, 1925, **30**, 513) found that the normal chlorid content of the spinal fluid is from 690 to 720 mg. per 100 cc. Low values are found in acute and tuberculous meningitis. The relation of spinal-fluid chlorids to blood chlorids is not constant, and a determination of blood chlorids is not necessary or useful in diagnosis. The normal protein content of the spinal fluid is from 30 to 80 mg. per 100 cc. It is increased in acute and chronic inflammations of the brain substance. In certain altered metabolic states accompanying infections of nephritis, some increase in protein can be expected. Spinal-fluid sugar should always be determined in relation to blood sugar. The normal relative value is from 40 to 60 per cent of the blood sugar. High relative values are found consistently in epidemic encephalitis, meningismus, convulsions, acidosis and nephritis, in poliomyelitis of the bulbar type and in a certain number of socalled normal cases. From the variety of cases in which a high relative value is found, it will be seen that this is not a reliable diagnostic point. Low relative values are found in acute and tuberculous meningitis with great regularity, and this is of considerable importance. The character of the toxin at work apparently determines to some extent the degree of general or selective change in chlorid permeability. Chlorids, protein and sugar are likely to vary directly with the acuteness of the infective process. They may bear some constant relationship to the disease itself. A knowledge of spinal fluid chemistry is helpful diagnostically in many conditions of the central nervous system. This is especially true in tuberculous meningitis and somewhat less true in purulent meningitis, encephalitis and polio myelitis. Calcium and phosphorus in the spinal fluid bear no relationship to their content in the blood or to the clinical picture of the patient.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

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The Eczemas of Bread Bakers and Confectioners.—WHITE (*Brit. J. Dermat. and Syph.*, 1925, **37**, 166) concludes from a dozen such eczemas that there is no eruption specific or distinctive of these industries and that they are incidents rather than consequences of the work. In an interesting experimental study upon himself and associates of the effect of the ingredients of flour upon the skin, the author found that salt (3 to 5 per cent in water), calcium phosphate and flour, mixed as a wet paste, produced a cutaneous reaction only if it were *kept* moistened; if applied dry there were no eruptions even after many days' exposure.

Mycosis Fungoides.—WILLS and HADFIELD (*Brit. J. Dermat. and Syph.*, 1925, **37**, 113) observed that the premycotic stage in a male, aged thirty-one years, started with a dermatitis compatible with a diagnosis of dermatitis herpetiformis, a similar feature previously reported by Pernet and Pringle. With peculiar periodicity in attacks and remissions, the premycotic stage changed suddenly to the tumor-formation period with enormous development of glandular and skin tumors and the patient died from asphyxia from an ulcerating tumor in the trachea.

The Interpretation of Mycosis Fungoides as a Variety of Lymphosarcoma.—FRASER (*Arch. Dermat. and Syph.*, 1925, **11**, 425) reports four cases of mycosis fungoides whose histologic picture he interprets as that of lymphosarcoma arising in the perivascular reticular system of the skin. Thus they are classed in the general group of the malignant hyperplasias of lymphoid tissue which may originate in different parts of the body found in many locations, such as the reticular tissue of the skin, submucous lymphoid tissue, lymph nodes and spleen, and could include the usual designated diseases, such as lymphatic leukemia, Hodgkin's disease, lymphosarcoma and mycosis fungoides.

Abnormalities of Blood-sugar Content in Eczema.—HALDIN-DAVIS and WILLS (*Brit. J. Dermat. and Syph.*, 1925, **37**, 364) found in about 66 per cent of 20 cases of eczema (excluding frank diabetics) that there was associated some abnormality in the blood-sugar levels, this consisting either of: (1) Abnormally high blood sugar during starvation or (2) appearance of abnormally high amounts of sugar in the blood soon after the injection of glucose (50 gm.). In many of these the

blood-sugar abnormalities were found when the eczema was widespread and accompanied by edema. Neither drastic nor moderate reduction of carbohydrates aided in producing clinical cures, save in those occasional patients where the consumption of sugar and starchy substances was exceptionally excessive.

Some Observations on the Fractional Method of Gastric Analysis in Diseases of the Skin.—In a series of 100 patients, 50 of which were acne rosacea and the other 50 acute widespread dermatoses, BROWN (*Brit. J. Dermat. and Syph.*, 1925, **37**, 213) performed fractional gastric analysis, and concluded that it is a clinical method of decided value in the investigation of dermatologic conditions, being more accurate than the single one-hour test. His finding of hypochlorhydria as a prevailing condition in rosacea (56 per cent) confirms that of Pyle and Barber (58 per cent), but the hypochlorhydria was not as extreme in degree. In other cases it was noted that hyperchlorhydria prevailed in acute widespread dermatoses. Furthermore, complete achlorhydria or extreme hyperchlorhydria may be present in dermatologic conditions without any gastric symptoms.

Fatal Case of Lupus Erythematosus, with Necropsy.—GIBSON (*Brit. J. Dermat. and Syph.*, 1925, **37**, 232) was unable to find any evidence of tuberculosis at the postmortem examination of a male, aged twenty-nine years, who died from acute lupus erythematosus. The recovery of the streptococcus from the blood during his life is of great interest; after death the only focus of infection found was the tonsils. No cardiac vegetations were found.

Effect of Bismuth on the Wassermann Reaction in Patients Unresponsive to Arsphenamin.—BELDING (*Arch. Dermat. and Syph.*, 1925, **12**, 334) found that a course of bismuth (oil suspension averaging twenty injections over ten weeks of approximately 1.33 gm. of metallic bismuth) reduced the Wassermann antibody in 37 per cent of a series of 35 patients, 10 of whom showed neurologic invasion and 3 vascular syphilis, the rest showing no evidence of activity. All had been treated by arsphenamin and mercury and were considered Wassermann-fast; the reduction under bismuth persisted during at least six months' observation.

GYNECOLOGY

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Inguinal Endometriosis.—In one of his more recent contributions to the interesting subject of endometrial implants, SAMPSON (*Am. J. Obst. and Gynec.*, 1925, **10**, 462) discusses what he calls inguinal endo-

metriosis, which in the past has been called by such names as endometrial tissue in the groin, adenomyoma in the groin and adenomyoma of the round ligament. In the 3 cases of inguinal endometriosis on which his study was based the structure of the endometrial elements was identical with that of those found in the uterine wall resulting from the direct invasion of the myometrium by the mucosa lining the uterine cavity. In all 3 cases the nodule in the groin reacted to menstruation as was indicated by its being tender at that time and also by the presence of cavities filled with blood and blood pigment in its tissues. In the first specimen the nodule was situated just below the external abdominal ring and the round ligament was not observed during the operation. In the second the mass of tissue which had reacted to the endometrial invasion was adherent to the side of the terminal portion of the round ligament, but he was unable to demonstrate the actual invasion of that structure by endometrial tissue, possibly because serial sections were not made. This tissue had evidently primarily developed in structures lateral to the terminal portion of the round ligament. In the third specimen the endometrial tissue occupied the region of a femoral hernia and was densely adherent to the anterior surface of the femoral vein. None of these 3 cases could be classified as a tumor of the round ligament, although the author believes that in all of them the endometrial tissue might have reached the groin through vessels accompanying the round ligament. In the first case peritoneal endometriosis was present. There was an endometrial invasion of the uterine end of the round ligament and the structures about it on the same side as the endometrial tissue in the groin near the distal end of that ligament. In the second case peritoneal endometriosis was also present with an invasion of the broad ligament of the same side as the endometrial tissue in the groin. In the third case gross evidence of peritoneal endometriosis was not present. The pelvic organs were inspected but were not removed. The uterus was slightly enlarged with a small leiomyoma presenting between the layers of the broad ligament of the same side as the endometrial tissue in the groin. The possibility of metastasis through lymph channels or veins reached by the invasion of the uterine wall by its mucosa must be considered in this instance, that is, from a primary uterine endometriosis or from endometrial tissue escaping into uterine vessels during menstruation. A study of the whole subject of pelvic endometriosis suggests that at times metastasis occurs through the lymph vessels and possibly through the veins and that endometrial tissue may reach the groin and other parts of the body through these channels. Future studies will demonstrate the truth or fallacy of this interpretation. The author believes that we are warranted in stating that possibly inguinal endometriosis may be secondary to that in the pelvis and that it may arise from: (1) Metastasis through lymph vessels invaded by endometrial tissue implanted about the uterine end of the round ligament and the broad ligament. (2) A direct extension or metastasis along the round ligament from a peritoneal endometriosis about the abdominal inguinal ring. (3) Metastasis from the direct invasion of the uterus or tube by their mucosa with extension to the superficial lymphatics and veins and also from endometrial tissue escaping into uterine vessels during menstruation. (4) Implantations in a hernial sac.

Removal of Stones from the Lower Ureter by the Vaginal Route.—A decision as to the method of choice for the removal of a stone which is partially or completely obstructing a ureter depends principally upon the location of the stone within the ureter and upon the predilection of the individual operator for one or another type of operation. LOWER (*J. Urol.*, 1925, **14**, 113) has found the vaginal route of value not only in multiparous but also in nulliparous women and even when the stone is so high in the pelvic portion of the ureter that its palpation is scarcely possible. It is always advisable to try nonoperative measures and cystoscopic manipulations before attempting operation. The author has used the vaginal route for the removal of ureteral stones successfully in 6 cases, while in 2 others he was not successful because the stone moved up the ureter during the manipulation to a point where it could not be reached through the vaginal opening. The technic of this operation is very simple: The patient is placed in the lithotomy position, the cervix is caught with a curved tenaculum and pulled well to the opposite side, thus pulling down the base of the bladder and the ureter. The stone is palpated and an incision is made through the mucous membrane of the vagina parallel to the ureter. The tip of the index finger is then pushed through this slit and the ureter and stone located. A tenaculum is then placed above the stone, to prevent it from moving up the ureter. By releasing the traction upon the cervix and by gentle traction on the tenaculum on the ureter, the ureter and stone are brought within the opening in the vaginal mucous membrane, at which point the stone can readily be removed through a longitudinal opening. The incision in the ureter is closed with a few fine absorbable sutures and the ureter released. A small cigarette drain is inserted through the vaginal slit and is removed at the end of the second day. If there is no leakage of urine, and there is not likely to be, the patient can leave the hospital three or four days after the operation. The advantages claimed for the method are that it is comparatively simple for removing a stone from a location which is often difficult by other methods; it affords independent drainage, it avoids an external incision and it shortens the period of convalescence.

The Leukocyte Count in Ectopic Gestation.—Anything that can aid in making the diagnosis of ectopic gestation in the doubtful cases is certainly of great value, and in order to determine what information can be derived from the leukocyte count FARRAR (*Surg., Gynec. and Obst.*, 1925, **41**, 655) has studied the records of 150 cases of ectopic pregnancy which had been operated upon in the Woman's Hospital in New York City. Summarizing her study, she states that in ectopic gestation the leukocyte count fluctuates according to the amount of fresh blood thrown into the peritoneal cavity and the rate of absorption. It tends to drop quickly to normal as the blood in the peritoneal cavity is absorbed or walled in; 48 per cent of the cases had a normal leukocyte count before operation was performed. The count was normal in 29 cases of unruptured tubal pregnancy in which there was no free blood and in 43 cases of ruptured tubal pregnancy in which the blood was walled in. The leukocyte count was an index to the amount of free blood in the peritoneal cavity and the polymorphonu-

clear count was increased markedly only in cases having fresh blood in the pelvis and increased in direct proportion to the amount of recent blood found at the time of operation. The fluctuating leukocyte count together with the moderate elevation of temperature differentiates ectopic gestation from a purulent salpingitis with its more uniformly high leukocyte count and fluctuating temperature. In cases of ruptured tubal pregnancy the steadily rising leukocyte count indicates active bleeding before the fall in the number of red cells or hemoglobin gives warning of the condition. The leukocyte count to be of diagnostic value must be taken at least daily and in critical cases even hourly and used in conjunction with the history and clinical findings in the case.

RADIOLOGY

UNDER THE CHARGE OF

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Cancer of the Tongue and Mouth.—SIMMONS (*Am. J. Roentgenol. and Radium Therap.*, 1925, **13**, 545) gives statistics to show that cancer of the buccal mucosa is very malignant and easily overlooked by the patient and physician. Chronic irritation has a definite relation to the etiology. Syphilis seems closely related to the etiology because different series give from 14 to 40 per cent positive Wassermann reactions in this type of cancer. All these growths are squamous-cell cancers, and clinically are divided into two classes: The papillary type, which is of relatively low malignancy, and the rapidly growing type, metastasising early, and often incurable inside of six weeks. Cancer of the mouth should be grouped according to malignancy when reported by the pathologist. Malignancy varies with the position, as carcinoma of the floor of the mouth is most malignant, while that of the lower jaw, cheek and upper jaw are relatively less so, in the order named. In early stages there are few or no symptoms, and all ulcers not yielding to removal of the cause and ordinary treatment after two weeks should be considered cancer. The author believes that surgery of some form followed by irradiation is the best treatment for these cancers. He divides the treatment into three types: Prophylaxis, such as oral cleanliness, early care of obviously benign growths, and if cancer is present attempt at radical removal, or palliative treatment for those definitely beyond cure. A summary of the methods used at the Massachusetts General and Huntington Hospitals is as follows: Morphin and morphin with atropin are given one and one-half hours and one-half hour respectively before the operation; ether is used for anesthesia by the pharyngeal tube method with the pharynx packed off. All cases receive postoperative Roentgen-ray treatment of glandular areas of the neck. Postoperative Roentgen treatment to the operative site has been abandoned unless at least two weeks has elapsed between treatment and operation, as otherwise the treating is apt to be unsatisfactory. In the inoperable types radium

"seeds" in the growth and Roentgen treatment to the glands of the neck give relief to the patient and prolong life. Out of 53 cases the author cites 30 per cent of cures of cancer of the mouth out of an operability of 65 per cent.

A Brief Review of the Indications and Technical Procedures Employed by the Authors in Treatment of Cancer of the Uterine Cervix and Body.—The vast majority of cervical cancers are epitheliomas, according to BURNAM AND NEILL (*Radiology*, 1925, **5**, 1), while in the body of the uterus adenocarcinoma is the most common. Treatment of these cancers depends on their stage of development, whether to be palliative or curative. In early cancers of the body of the uterus they advise hysterectomy unless there is some definite contraindications to surgery when curative procedures with radium should be instituted, such as up to 2½ gm. hours of intrauterine radiation. In borderline cases they would advise hysterectomy when possible, as efficient radium application is difficult to estimate. However, if surgery is contraindicated 3 gm. hours or more combined with external through-and-through treatment should be palliative only, giving 1 or 2 gm. hours combined with external radiation. The authors see no value in preoperative radiation, but do advise postoperative treatment to begin in four weeks by direct treatment to the vaginal vault and cross-firing over the iliac glands. In cancers of the cervix in early cases they advise surgery with preradiation, although in some cases one or the other method alone is advisable. The preliminary radiation consists of 1 gm. hour in the cervical canal and 1 gm. hour covering the entire cervix. The sooner the operation can follow the better, preferably the next day. Postoperative radiation is not advisable except in recurrences. In borderline cases, when the growth involves the vaginal wall or parametria, but is freely movable, there is probably more general combinations of surgery and radiation indicated than in early cases. Here radiation is given with a flat applicator to the involved portion of the vaginal wall, 1 gm. for thirty minutes to each square inch of surface, applied direct with a filter of 1 mm. of brass and 2 mm. of rubber. If radium alone is given it is for 3½ gm. hours in a single treatment, as a single dose is better than broken doses. As a rule, growth disappears locally. A second treatment is not given except in new development. In the borderline cases of cancer of the cervix where there is some fixation operation is not to be considered. The radiation is the same as in the former group, but in addition a strong emanation point is implanted centrally into the involved parametrium. The authors feel that Roentgen-ray radiation has no place in these cases except as a palliative measure in the more advanced types.

Roentgenography of Hydatid Cysts of the Lung.—HEUSER (*Am. J. Roentgenol. and Radium Therap.*, 1925, **13**, 529) reports a case of hydatid cyst of the lung which was diagnosed by Roentgen ray and operated upon. The diagnosis is not always easy and the prognosis with surgery varies with the location in the lung. Sarcoma of the lung is very similar to a cyst, and about the only difference is that in the roentgenologic examination the cyst appears less dense than the sarcoma. Pleural effusion may complicate a cyst in the lower lobe and then the diagnosis of cyst may be very difficult, but is aided

by change of positions in making the examination. In a second case the author shows how it may be impossible to make a clinical diagnosis of pulmonary cyst and the importance of careful attention to roentgenologic findings. He cites cases also to show how pleurisy may complicate the diagnosis of hydatid cyst, that cysts may complicate tuberculosis and cardiac lesions. After operation the case should be followed by roentgenologic examinations in case new cysts may develop. Cysts of the lung may occur with those of the liver and this should be borne in mind so as to make the examinations from all possible positions.

NEUROLOGY AND PSYCHIATRY

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The Average Sex Life of American Women.—Because of the present inadequacy of sex knowledge, a plan was evolved for coördinating the activities of a number of societies that might contribute materially to this problem. DICKINSON and PIERSON (*J. Am. Med. Assn.*, 1925, **85**, 1113) present the first of a series of articles that are to appear on sex problems. In making some investigations on contraceptive measures, the following scientific needs were brought out: "Age at marriage and age at childbirth for American women, duration of reproductive life, fecundity and fertility, findings that point to a diagnosis of sex experiences, exact genital measurements, anatomy of sex act and the bearings of it on health, correlation of pelvic disorders and diseases with sex practices of all kinds." The work of Davis on autoerotic practices in women, published in *Mental Hygiene* (July, 1924, and January, 1925), is reviewed as a preliminary to the article. Two-thirds of these women, of average age thirty-seven years, unmarried, report the practice of masturbation. The average age of beginning masturbation was between eight and nine years, well before puberty. The percentages of those indulging in perverse sex acts is given. Of a group of married women, of average age thirty-eight years, the median age of marriage was twenty-five and seven-tenth years. Two-thirds of these experienced pleasure in sex relations after marriage; one-third showed alteration in feeling thereafter, being about equal as regards gain or loss. One in 20 mentioned reception of information on birth control. One-fourth of them continued masturbation after marriage. Fear of pregnancy was rarely present. The sexual impulses of husbands were estimated to be greater in 62 per cent, less in 3.5 per cent and equal in 31 per cent. Coitus occurred on an average of twice a week in the group. Fig. 1, charts for women of temperate climates; the

average ages of onset of autoeroticism, nine years; onset of menses, fifteen years; age of marriage, twenty-four years; menopause, forty-nine years. Average clitoris measurements are given in Fig. 3. To the conventional classification of vaginal orifices: (1) Intact unentered hymen (virgin); (2) married nullipara (wife or cohabiting imparous single women; (3) parous women; the authors add (4) nulliparous orifice of very vigorous coitus; (5) the virgin orifice massaged to various dimensions, some among the largest; (6) the parous orifice that seems to owe its immunity from hymen damage or tear of pelvic floor to the oft-repeated stretch of one or both foregoing experiences. Measurements were made with glass balls of varying size inserted, or with various test tubes or glass cylinders inserted. A chart is given showing various measurements in centimeters. Much stress is placed on palpation of the sharp edge of the hymen. A large percentage (73) of Davis's group approved of contraceptive measures and practised them. These unions averaged 1.9 children and 2.5 pregnancies each. Figures for true sterility are not definite, but it is the opinion they are high. The authors are attempting to study the methods of birth control in foreign countries.

Comments on the Pathology of Dementia Precox.—The lack of uniformity of concept about dementia precox makes it difficult for pathologists and clinicians to agree on findings. Schizophrenia refers to the mental mechanism of some cases, and is sometimes used synonymously with dementia precox. LEWIS (*J. Nerv. and Ment. Dis.*, 1925, **62**, 225) quotes Child concerning the old problem of organic and functional: "The relation between structure and function in the organism is similar in character to the relation between the river as an energetic process and its banks and channel." Literature is cited dealing with findings of the brain and endocrine organs in dementia precox and with the most common clinical findings. The author reviews nine old cases of dementia precox that came to autopsy. Meager clinical material is assembled. The cases showed gradual deterioration, usually from youth. Most of the reports were concerned with autopsy findings. Small hearts and hypoplastic aortas were the rule. Several patients had severe pulmonary tuberculosis. Some compensatory changes had occurred in the endocrine organs in a few. These are discussed. The frequency of pulmonary tuberculosis in dementia precox is explained by the theory of Rokitansky, who believed that valvular disease of the right side of the heart tended to favor the development of chronic phthisis. On the other hand, patients suffering from valvular disease of the left side of the heart are not prone to have pulmonary phthisis. Whether the small heart found in patients with pulmonary tuberculosis is primary or secondary to the disease is open to question. The author feels that in dementia precox the small heart is primary and tuberculosis of the lungs is secondary to the hypoplastic heart and aorta. From a biochemical standpoint literature is cited to show that decrease in blood uric acid in dementia precox has been found but not constantly. Catatonic cases show some tendency to increased blood sugar. The average variability of blood chemistry is greater than in normal persons, showing probably a labile metabolism. It is felt, but is by no means certain, that hypoöxidative processes are

predominant. This bears out work in which basal metabolism was below normal in 50 per cent. A Russian neurochemist has isolated many enzymes from the gray matter of brains of normal people. This opens up new fields. Treatment is reviewed. Where malarial treatment, as for paresis, has been tried no lasting results were obtained. General reëducational and hygienic measures are recommended, including physiotherapy, occupational therapy, etc. Sterile meningitis from intraspinous injection of inactivated horse serum has been induced with apparent improvement in a few cases. The Steinach rejuvenation operation has been tried with negative results. Narcosis induced over several days by special drugs has been reported by European investigators. This method has not been used in America. As yet it has not been given adequate trial. Psychoanalysis is attempted with varying results. The writer seems to lean to the view that true dementia precox is an organic condition intimately associated with hypoplasia of heart and aorta. The hope for treatment, if any, lies in childhood. An excellent bibliography is appended.

Cerebrospinal Fluid Pressure from the Clinical Point of View.—AYER (*Arch. Neurol. and Psychiat.*, 1925, **14**, 440) makes a plea for accurate manometer readings of spinal fluid pressure with every lumbar puncture. He prefers the aqueous manometer used with a three-way stopcock interposed between the needle and the manometer. Two lengths of 350 mm. each should be available. The mercury U tube has one advantage in that negative pressures may be read with it. The estimation of drops of fluid per minute or spurt of fluid are to be condemned as unreliable for telling fluid pressure. Normal fluid pressure from the lumbar sac varies between 100 and 200 mm. of water. He regards pressures from 200 to 250 as suspicious and 250 to 300 definitely abnormal. Such pressures are taken with the patient lying on side with head in alignment. In this position cisterna magna and ventricle pressures are the same as lumbar pressures. In sitting posture the lumbar pressure is about doubled, while cisterna magna and ventricle pressures are negative. Holding breath, sneezing, grunting and cramped position tend to elevate the pressures. A feeling of faintness is usually accompanied by lowering of pressure. Compression of jugular veins—Quechenstedt's sign—causes an increase in the pressure unless there is more or less complete occlusion of the subarachnoid space. In very low pressures and when the neck was compressed enough to interfere to cause the patient to cough the author failed to get the usual jugular response and mentions these as sources of possible error. The latter gave an apparent jugular response in a cord-tumor case. A failure of response to compression of a jugular on one side in the absence of possible cord tumor might indicate a lateral sinus thrombosis on the same side. There is no marked correlation between spinal fluid pressure and blood pressure, but the tendency is for a higher fluid pressure in hypertension. Factors that affect the spinal fluid pressure are: (1) "Elasticity of dura mater; (2) intracranial arterial pressure; (3) intracranial venous pressure; (4) secretion pressure of cerebrospinal fluid; (5) rate of absorption of fluid; (6) brain bulk or amount of solid substance in the cranium; (7) hydrostatic pressure provided the patient is in any position other than the

horizontal." Highest pressures even up to 1000 mm. of water, may be seen in acute meningitis brain tumors hydrocephalus and hemorrhage. High pressures may also be seen in uremia polycythemia, cerebral thrombosis and brain abscess. Low pressures are seen in fainting and shock. The pressure is often low in headache after lumbar puncture also in long-standing degenerative diseases of the nervous system. Valuable diagnostic information may be had by studying the pressure from two sources at once and by studying the change in pressure with the withdrawal of fluid. Ayala's index is given and may be useful in diagnosis.

Comparison of Gold Chlorid, Benzoin and Mastic Tests on Cerebrospinal Fluid.—COCKRILL (*Arch. Neurol. and Psychiat.* 1925, **14**, 455) studied 400 routine spinal fluids from 334 patients by the three methods. The cases comprised neurosyphilis, syphilis without nervous system involvement, nonsyphilitic and various pathologic conditions, as meningitis, multiple sclerosis and general medical cases, including many nonsyphilitic neurologic conditions. In 384 instances the three tests gave similar reactions; in 16, dissimilar. The author feels that the benzoin test is simpler for routine examination but in certain diseases, as meningitis and multiple sclerosis, the colloidal-gold test is preferable. A table of data summarizing the study is given.

PATHOLOGY AND BACTERIOLOGY

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Proliferative Reaction to Stimuli by the Lytic Principle.—The arguments in favor of a reaction of proliferation in the presence of the lytic agents are put forth by HADLEY (*J. Infect. Dis.*, 1925, **37**, 35), giving further support to the observations made by d'Herelle and Bordet and Cuica. The latter workers, however, used liquid media, which seems a less precise method of estimating the growth than agar, as employed by the author. Bacillus pyocyaneus was the organism studied, and it was found that the lytic agent being present, two types of colonies grew, the more rapidly growing, the L. colonies, were subject to the appearance of irregularities and clearing areas, evidencing lysis, while the other type, the R. colonies, seemed insusceptible to this action. The lysed colonies demonstrated "transmissible lysis," while the R. colonies showed the presence of no such agent on transfer. Although the evidence of the lytic phenomenon in the Bacillus pyocyaneus cultures differs widely from that pictured by d'Herelle working on the Shiga bacillus, nevertheless the author urges that it is but

another manifestation of bacteriophage. The interrelationship between organism and lytic principle seems in the nature of host and parasite, to which the host organisms develop a varying degree of resistance, which is of three orders: (1) Those absolutely susceptible to lysis; (2) those with a moderate degree of susceptibility to the lytic agent; (3) a resistant type, as illustrated by the R. colonies. It would appear that the function of the lytic agent is as much to stimulate the multiplication of the host, perhaps to insure its own future, as to carry on lytic action. This proliferative action is claimed by the author to be no evidence of the bacteriophage being an ultravirus, as upheld by d'Herelle for he points out that soot and creosote also stimulate the same proliferative response. In conclusion the article urges that the nature of the lytic agent be not finally considered as a living corpuscle but judgment should remain open to the possibility of its being either chemical or mechanical. Also this phenomenon is not to be confined to the colon-typhoid group, but should be regarded as varying in manifestation in several other groups of organisms.

Cholera Vibrion Statistically Studied as to Form and Growth.—To meet the assertions of those workers who claim that the pleomorphism shown by the cholera vibrion and other bacteria is an evidence of a complicated life history, HENRICI (*J. Infect. Dis.*, 1925, **37**, 75) has put forth carefully taken data to show that the variation in contour is to be correlated with the rate of growth. A five-day beef extract culture of the cholera vibrion, which showed the complete range of described forms, was used for transfer to uniform agar slants. These tubes were sampled at regular intervals up to ten days, and in each case the growth was analyzed as to enumeration, size and shape of the organisms, the results being obtained by special methods, devised by the author. All forms of the organism were noted during the period of sampling, viz: bacillary, vibrion, spherical and budding types. The bacillary form was found to be predominating up to thirty-six to forty-eight hours, at which time the numbers were at their height after which the more irregular forms showed a progressively greater frequency. The spherical form was found to be in the majority when the bacterial numbers were declining. The budding types stained with Congo-red, an indication of dissolution and not a reproductive stage. The conclusion followed that the pleomorphism so characteristic of this organism is to be ascribed entirely to the rate of growth; during the phase of positive acceleration the bacillary forms predominate, while during the phase of negative acceleration the vibrion, spherical and budding forms are in the ascendency.

Bacterial Factors in Pyorrhea Alveolaris.—In an attempt to discover the causative agent in pyorrhea alveolaris a great many studies on the bacterial flora of the mouth have been undertaken. Miller (1890) found butyric acid without discovering the causative organism; Rodella (1905) isolated Bacillus putrificus, which was confirmed by Kligler, but sugar fermentations of these show this to be an inclusive group; in 1917 Hall obtained Bacillus bifermentans in association with streptococcus, and many more isolations have been reported. The experiments reported by HALL (*J. Infect. Dis.*, 1925, **37**, 88) were undertaken

to determine if sporulating anërobes were to be found in the mouth. Saliva was taken from 43 persons after breakfast, before brushing the teeth, and 1 cc. inoculated into brain medium, which was heated to 80° C. for twenty to thirty minutes, to destroy all but the spores. In only 6 cases were anërobes found, four distinct organisms: Bacillus welchii, 3; Bacillus bifermentans, 1; Bacillus tetanomorphus, 1; Bacillustetani, 1. In 3 of these cases caries was present. None of these anërobes were found to appear in successive cultures and no definite association of them with pyorrhea could be ascertained with the possible exception that some anërobes may cause irritating calculus depositions from the saliva.

Yeasts from Human Sources.—In view of the interest evoked by the yeasts of sprue and thrush, the work of PECKHAM (*J. Infect. Dis.*, 1925, **37**, 53) is significant in pointing out that of 51 yeasts obtained from human sources (mouth, throat, bronchi and vagina) 41 were pathogenic, the majority of these coming from the oral region. These yeasts were tested by inoculation into the groin and peritoneum of guinea pigs, producing local and disseminate abscesses, throughout the internal organs. One yeast was taken for intravenous inoculation of two rabbits and a blood-picture change resulted, of prompt lymphopenia, a secondary anemia and endothelial-cell proliferation. The immunized rabbits showed antibody formation but no glycosuria nor albuminuria. The immunized guinea pigs, on metabolic studies, showed a diabetic condition, while the postmortem finding in the more chronic infected cases was an extensive fibrosis of the islands of Langerhans. The author suggested that this may indicate a possible means of producing diabetic animals. THOMAS (*J. Infect. Dis.*, 1924, **35**, 407) showed the frequency of infections in guinea-pigs by organisms of the enteritidis-paratyphoid B group after exposure of the animals to cold, injection of other bacteria and in untreated animals, and also that striking changes were to be found in the islands of Langerhans in these animals. Menten demonstrated that these hydropic degenerative changes are correlated with variations in blood sugar. Such findings must be considered in interpreting results of experimental injections particularly in guinea pigs.

The Typhoid-Paratyphoid Group in Water Supplies.—As a result of the discovery of Bacillus paratyphoid B in various material during an investigation of an epidemic at Steinau, KAPELLER (*Centralbl. f. Bakteriol.*, 1925, **96**, 8) showed that with comparatively small amounts from the city water supply the presence of a Bacillus paratyphosus B was readily demonstrated. At the time of the examination of the water the epidemic was over and no cases of the disease existed. Therefore the literature was covered to find instances of water contamination with the typhosus-paratyphosus group. Kacyznski (1912) found eight typhoid bacilli in a liter of the Lemberg water supply, and therefore urged a more careful investigation, from a bacteriologic standpoint, of all water supplies. The incidence of contamination with this group of organisms is shown by the findings of 34 workers, widely scattered throughout the world, of 37 infected water supplies, as reported up to 1922. Of this number 33 contained typhoid bacilli, 4 Bacillus

paratyphosus B and 2 Bacillus paratyphosus A. Two of the Bacillus typhosus were in combination with Bacillus paratyphosus B. The finding of these bacteria was usually in isolated samples, and could not be demonstrated on daily examinations. This, together with the relatively long incubation periods of the considered diseases, added to the difficulty of correlating results. This accidentally discovered contamination with typhosus-paratyphosus group of bacteria without the association of an epidemic, and the comparative frequency of finding this group of bacteria as reported in the literature points to the necessity of a closer laboratory vigilance of water supplies.

Mechanical Irritation as Etiologic Factor of Cancer.—ALTER (*Am. J. Pathol.*, 1925, **1**, 511) reported a case which appears to present a striking example of mechanical irritation as an etiologic factor in the histogenesis of cancer. This case was that of a man, aged sixty years, who for one year previously had increasing constipation, loss of weight and finally obstruction. Operation revealed a new growth in the sigmoid. This growth was an annular type of carcinoma. Fitting into the lumen of the constricted portion with a ball valve-like action was the head of a long pedunculated polyp. The stalk of this was 8 cm. in length. Above the constricted ring was a saccular dilatation of the bowel, and in this was lodged a peach stone. This part of the gut was much thickened. Both polyp and cancer showed signs of chronic inflammation. The bowel was resected, and the man is alive and well five years afterward. The suggestion is made that the polyp arose as a sequel to an inflammatory process. Hypertrophy of the bowel followed its continuous attempts to get rid of the polyp. The irritation caused by the head of this pedunculated growth hitting against the wall started the cancerous growth. Lodgment of the peach stone above the growth and the extra efforts to get rid of it caused the saclike dilatation of the gut.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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Irradiated Foods and Irradiated Organic Compounds.—STEENBOCK and DANIELS (*Jour. Am. Med. Assn.*, 1925, **84**, 1093) state that by exposing such food materials as wheat, rolled oats, corn, hominy cream of wheat, shredded wheat biscuits, corn flakes, patent wheat, flour, cornstarch, meat, milk and egg yolk to ultraviolet light they can be endowed with rickets preventing properties. That such a wide

variety of foods can be thus affected appears to be due to the fact that practically all naturally occurring foods contain lipoidal constituents of the nature of sterols which can carry this activation. Cholesterol, for example, as obtained from brain is entirely inactive, but after exposure to ultraviolet light becomes rickets preventing. As fats are good solvents for these lipoids, practically all fresh fats, such as butter fat, olive oil, lard, corn oil, cocoanut oil and cottonseed oil, can be activated, often to a degree to make them compare favorably with cod liver oil. As antirachitic action consists in the induction of calcium assimilation and its conservation for the animals, this is a matter which concerns not only the young but also the adult. It is suggested that these findings may have their significance not only in nutrition, but also in the therapy of those diseases known to respond to irradiation with ultraviolet light.

The Cultivation of Endameba Histolytica.—Boeck and Drbohlav (*Am. Jour. Hyg.*, 1925, **5**, 371) obtained in culture from two cases of amebiasis two strains of endemeba. These were morphologically identical with the endameba in the feces of the patients and with Endameba histolytica. The "K" strain was grown in cultures for eight months and eleven days and the "E" strain for three months. The most suitable artificial environment for the growth of Endameba histolytica was in either the L. E. S. (Locke egg serum) or L. E. A. (Locke egg albumen) medium, at a temperature of 37° C. An initial reaction of the medium of pH 7.2 to pH 7.8 is necessary. The cultivation experiments demonstrated that Endameba histolytica may eat bacteria in the absence of a preferred diet of tissue juices, extracts and red blood cells. Both strains isolated in cultures proved to be pathogenic for kittens in which they produced acute dysentery, colitis and in two kittens a liver abscess. The virulence of the amebæ was not influenced by prolonged cultivation. These experiments confirm the work reported by Cutler (1918) with respect to the cultivability of Endameba histolytica. The authors, however, were unable to produce encystment under the conditions through which he claims to have brought it about. Their own media proved to be more suitable for the multiplication of Endameba histolytica than the blood bouillon medium. Encystment occurred in a culture of the "E" strain of Endameba histolytica on only one occasion. The L. E. S. and L. E. A. media have proved suitable for the cultivation of Endameba histolytica, Chilomastix mesnili, Trichomonas confusa, Chilomastix gallinarum, Trichomonas gallinarum, and has maintained Endameba coli and Endolimax nana for a period of three days.

The Relationship of Hard Water to Health: I. Hard Water as a Possible Factor in Urinary Concretion Formation.—Myers (*J. Infect. Dis.*, 1925, **36**, 576) states that oxamid fed to rabbits produced only a slightly larger amount of solid material in the urinary bladder when the rabbits received hard water than when they were given distilled water. Glass beads placed in the kidneys of dogs produced concretions with both a hard and a distilled water intake. Glass beads in the kidneys of albino rats failed to produce concretions with either type of water. No definite relationship was observed between hardness of the water intake and the amount of calcification of cartilage

blocks in the bladders of rabbits in conjunction with either a high- or a low-calcium diet. No evidence has been found proving hard water to be an etiologic factor in urinary concretion formation.

Complexity of the Scarlet-fever Toxin and Antitoxin.—PARK and SPIEGEL (*J. Immunol.*, 1925, **10**, 829) state that the fact that an individual convalescent scarlet-fever serum neutralizes the toxin of a certain scarlet-fever streptococcus in certain susceptible persons and not in others proves that the toxic filtrate has more than one toxin and that a person may be susceptible to one component and not to another or others. We can conceive that the usual scarlet-fever strain makes a toxic filtrate containing the different toxins A, B, C and D. A less common strain A, C, D, E or B, C, D, E. Strains from some septic sore throats, C, D, H, I, and from some erysipelas cases, C, D, K, L. Antitoxins to a greater or less degree would develop in any person or animal injected with any toxic filtrate to neutralize the actual toxins present in the filtrate. The finding that a certain convalescent serum or antitoxin horse serum will fail to neutralize a toxin for certain persons in the same quantity which is successful in others, but in larger amount succeeds, proves that the antitoxic response is different for the different component toxins either because of the different proportions of the toxins in the filtrate or because the child or animal responds differently in degree to the stimulus of the different toxins. We have the analogy of horses receiving the same amount of diphtheria and tetanus toxin. Some produce strong antitoxin for diphtheria but weak for tetanus and others strong antitoxin for tetanus but weak antitoxin for diphtheria. A convalescent scarlet-fever serum from a single patient may fail to cause blanching in a true case of scarlet fever because the two cases are due to two strains that differ in at least one toxin and so in one induced antitoxin. It is also probable that there are strains of streptococci that have the power to produce scarlet rash, producing toxins which are quite different from the standard Dick strains, so that after convalescing from infection due to one strain a second infection might occur from the other strain. Every year a few cases sent into the hospital with the diagnosis of scarlet fever after recovery develop a second attack. We have been inclined to think that the first attack was not scarlet fever, while if we had made a culture, possibly a strain of streptococci that made different toxins from the usual cases would have been found. If this assumption is true a case of scarlet fever at onset might give a negative Dick test to the Dick strain toxin, and its serum would then neutralize the standard toxin and blanch the rash of an ordinary case of scarlet-fever. The point is that it is not safe at the present time to limit the diagnosis of scarlet fever to cases due to the usual strains making the standard group of toxins. At most, the exceptional strains cause only a small minority of the cases of scarlet fever. Cases that do not respond to the serum should be studied carefully to determine whether their strains are typical ones. It is possible that in these a polyvalent antitoxic serum is indicated, or it may simply be that the scarlet fever streptococci or other streptococci or other microörganisms have invaded the deeper tissues and are beyond the help of antitoxins. Further investigation is necessary to determine the value of a bactericidal serum in these cases.

PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF NOVEMBER 16, 1925

The Fate of Ingested Benzoic Acid in the Dog.—ARMAND J. QUICK (from the Department of Physiological Chemistry, University of Pennsylvania). Since most of the studies of benzoic acid conjugation have been carried out on animals which excrete benzoic acid quantitatively as hippuric acid, little attention has been paid to other conjugation products of benzoic acid. Past studies on the dog, however, have indicated that the production of hippuric acid is comparatively small and that the urine, following benzoic acid administration, contains glycuronic acid. Owing to inadequacy of the analytic methods available, no quantitative studies of the relationship of hippuric acid, benzoyl-glycuronic acid and free benzoic acid have been made. Analytic procedures were devised for the direct determination of hippuric acid and of benzoyl-glycuronic acid, and these methods were then employed in the study of the conjugation of benzoic acid in the dog. It was found that ingested benzoic acid was completely conjugated and excreted partly as hippuric acid and partly as benzoyl-glycuronic acid. The quantity of hippuric acid, however, was comparatively small and relatively fixed in amount, while the benzoyl-glycuronic acid was variable, depending upon the quantity of benzoic acid in excess of the organism's capacity of synthesizing hippuric acid. Exogenous glycine, either free or combined, caused a definite but small increase in the production of hippuric acid. These findings emphasize the importance of the glycuronic acid conjugation of benzoic acid, and the limitations of the hippuric acid synthesis in dogs even when the organism is offered large quantities of exogenous glycine.

The Growth of the Nervous System and the Behavior Pattern.—G. E. COGHILL (from the Department of Anatomy of the University of Kansas). The work upon which this report is offered has been made upon embryos of amblystoma. It represents an effort to analyze the nervous system upon the basis of behavior and to explain behavior upon the basis of nervous structure. It is hoped that the following conclusions may be of interest to physiologists: (1) The behavior pattern of amblystoma develops according to a regular order of sequence of movements. The muscles of the embryo are a longitudinal series of segments (myotomes). The first movement is a contraction of the anterior muscles (flexure). Progressively in time the contraction extends farther through the series of muscles until finally the entire series on one side only contracts and causes the animal to assume a tightly coiled condition (coil reaction). This signifies the attainment of full power of contractility by the muscles. Any particular movement begins in the anterior region and progresses tailward, according

to the order of its embryologic development. During the coil stage the movements are almost universally away from the side stimulated (avoiding reaction). Up to the coil stage there has been simply a gradual development of the flexure to its extreme limit, the coil. There then appears instantaneously a new pattern in the reaction: a flexure, beginning at the anterior end and progressing caudad, is followed by a second flexure in the opposite direction before the first has reached the caudal end of the system. Such movements in series, each pressing backward upon the water, produce locomotion (the swimming reaction). (2) This behavior has a definite and specific counterpart in nervous organization, and the order of development in structure explains the order of development of the behavior. The motor axones are collateral branches from descending tract axones. Stimuli can enter this tract only in its anterior part because afferent neurones undergo synapse, not with motor neurones of the same side, but with commissural neurones which exist only in the anterior region. This arrangement insures crossed reflexes and anterioposterior (cephalocaudal) progression of muscular contraction. The first reactions are made possible by the growth of the commissural cells between an already existing sensory tract of one side with an already excisting motor tract on the other. The instantaneous appearance of the swimming reaction in perfect form is explained by the growth of collaterals from the axones of anteriorly located tract neurones into synapse with the commissural cells so that an excitation that is passing directly to the muscles of one side is shunted off to the muscles of the other, but delayed in passage by the intercalation of at least one additional neurone in the course. (3) The functioning neurone is a growing structure, and its growth extends its own function and that of the nervous system as a whole. This is shown not only by the instances cited above but particularly by the motor root fibers. Many of the motor roots, after the muscles (myotomes) have acquired full function in locomotion, consist of only one fiber. This fiber branches with sufficient profusion over the muscle to innervate all of its cells, while the terminal branch of the fiber is growing entirely beyond the muscle into the primordium of the limb, and at a time long before limb muscle is differentiated. The growth of functional neurones into nonfunctional primordia opens an important field of inquiry, bearing, as it does, upon problems of physiology, pathology and hygiene. (4) There is a pronounced periodicity in the development of sensitivity (investigations jointly with Dr. R. W. Watkins). This may be due to alternation of periods of growth with periods of function in the nervous system. Since embryos from the same batch of eggs conform in the main to the same rhythm, the periodicity would seem to have its inception at the time of fertilization of the egg. (5) The motor mechanism of amblystoma is probably the prototype of integrating mechanisms in mammals. The ventral horn neurones of man are longitudinally oriented (Lhermitte and Kraus) and collaterals go from their axones back into the gray. The motor cells that integrate arm flexion (analogous to trunk flexure in amblystoma) are distributed through five cord segments. Longitudinal conduction through this column of cells by means of the axone collaterals, the fasciculi proprii or the longer tracts may be the mode of integrating muscles for elementary components of the behavior pattern.

The Kinetics of Osmotic Swelling in Arbacia Eggs.—MORTON MCCUTCHEON and BALDWIN LUCKE (from the Laboratory of Pathology, School of Medicine, University of Pennsylvania, and the Marine Biological Laboratory, Woods Hole, Mass.). The volume of living cells is conditioned by a number of factors, an important one being the concentration of the surrounding medium with which the cell contents are in dynamic osmotic equilibrium. In order to study the rate of volume change resulting from osmotic changes, and the conditions that influence this rate, it is necessary to use *isolated* cells, the viability of which can readily be tested. An almost ideal cell for such an investigation is the unfertilized egg of the sea urchin. In the present study it is shown that the rate of swelling of these cells follows well-known diffusion laws, but that because of the presence of a semipermeable membrane enveloping the cells, other factors than diffusion come into play. The regularity with which the various processes pursue their course is such that events may be calculated; it is found that a good agreement exists between the observed and the calculated results. The rate of swelling of arbacia eggs in hypotonic sea water, over wide ranges of temperature and concentration, is found to follow the equation $\frac{dx}{dt} = k\,(a - x)$, when a is the difference in volume of the cell at the first instant and at equilibrium, x the volume change up to a time, t, and k the velocity constant. (See R. S. Lillie: *Am. J. Physiol.* 1916, **40**, 249.) The rate of swelling, while primarily regulated by diffusion forces, is influenced also by other processes occurring in the semipermeable membrane. Evidence for this assertion is furnished by the effects of temperature and of concentration on the rate. Calculations made from the values of k at various temperatures show that the temperature coefficient is high, from 2 to 3, for a change in temperature of 10°, corresponding to a chemical rather than to a diffusion process. Calculated from the Arrhenius equation, the heat of activation ranges from 12,000 to 19,000 calories. The rate of swelling is greatly affected by the osmotic pressure of the sea water, and in a way not explainable on the grounds of a pure diffusion process. It requires very much longer for the cells to reach equilibrium in a mixture of 40 parts of sea water to 60 of distilled water than when 80 parts of sea water to 20 of distilled water are used. There is a corresponding change in the velocity constants. In a typical experiment at 15° C. the value of k in 20 per cent sea water was 0.006; in 40 per cent sea water, 0.012; in 60 per cent sea water, 0.024; in 80 per cent sea water, 0.072. On these grounds it is concluded that processes of unknown nature occur in the semipermeable membrane, and modify the effects of diffusion.

Studies on the Inorganic Composition of Blood.—S. E. KERR (from the Department of Physiological Chemistry, School of Medicine, University of Pennsylvania). After hemorrhage the blood volume is restored by the inflow of body fluids. The composition of the diluted blood will vary, however, depending upon the source of the diluting fluid. Water from the gastrointestinal tract will cause a diminished concentration of all the constituents. Lymph will cause a decrease in the potassium and possibly protein of serum. Intracellular fluid, such as that of muscle (the water and inorganic salts) is low in sodium and

chlorid and high in potassium and magnesium and, therefore, might cause a decrease in the sodium and chlorid and a rise in the potassium and magnesium concentrations of serum. A study was made with the hope of obtaining information concerning the main source of the fluid which restores the blood volume after hemorrhage. Determinations of specific gravity, water, sodium, potassium, chlorids and inorganic phosphates were made in serum and corpuscles; calcium, magnesium and protein in serum alone. Improvements were made in the methods for estimating sodium and potassium. A single hemorrhage, amounting to from one-third to one-half of the total blood volume resulted in a slight decrease in both sodium and chlorid of serum, and no significant change in corpuscles. Repeated severe hemorrhage produced a greater fall of sodium and chlorid of serum, a large increase in the potassium concentration of the corpuscles and an increase in the inorganic phosphate of serum. No changes in the potassium, calcium or magnesium of serum were observed. These observations, together with other indirect evidence obtained from the literature, indicate that a considerable part of the fluid entering the blood stream after hemorrhage comes from within the tissue cells. With hopes of obtaining an explanation of the unexpected rise of potassium in corpuscles after hemorrhage other experimental procedures were studied. The concentration of potassium of the serum was diminished by bleeding and infusing a solution of gelatin and sodium chlorid. The potassium concentration of the corpuscles rose more rapidly than with bleeding alone. Overdosage with insulin resulted in a fall of serum potassium and a rise of cell potassium. Subcutaneous injections of sodium oxalate caused a large increase in serum potassium with a corresponding increase in the corpuscles. It seems most probable that in all of these experiments potassium has permeated into the red cell, an observation contrary to the general teachings at present. The forces controlling the curiously unequal distribution of potassium between plasma and corpuscles are obscure.

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